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(71) Applicant: GENZYME CORPORATION [US/US]; One Mountain Road, Framingham, MA 01701 (US).

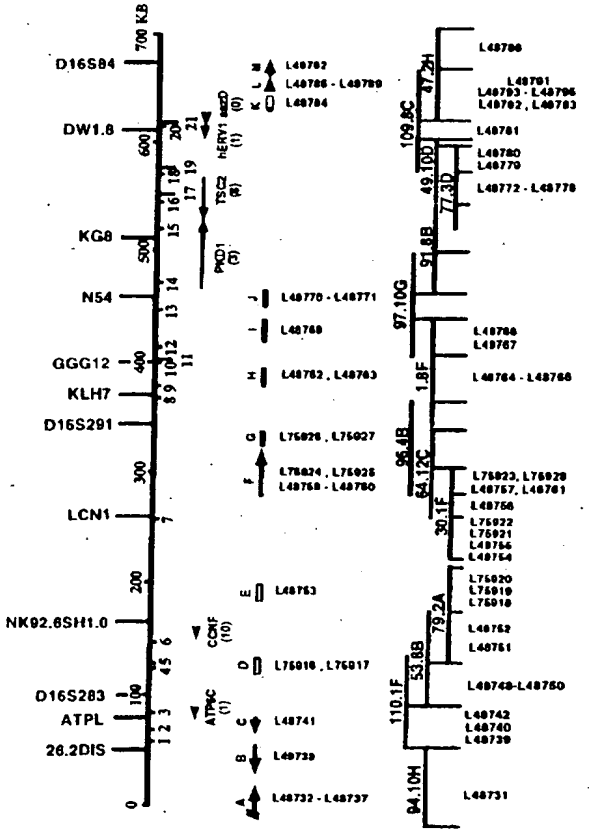
(72) Inventors: LANDES, Gregory, M.; 19 Indian Meadow Drive, Northborough, MA 01532 (US). BURN, Timothy, C.; 3 Adams Road, Northborough, MA 01532 (US). CONNORS, Timothy, D.; 304 Hayden Rowe Street, Hopkinton, MA 01748 (US). DACKOWSKI, William, R.; 4 Valentine Road, Hopkinton, MA 01748 (US). VAN RAAY, Terence, J.; 43 Worcester Avenue, Hudson, MA 01749 (US). KLINGER, Katherine, W.; 54 Bowditch Road, Sudbury, MA 01776 (US).

(74) Agent: DUGAN, Deborah, A.; Genzyme Corporation, One Mountain Road, Framingham, MA 01701 (US).

(54) Title: NOVEL HUMAN CHROMOSOME 16 GENES, COMPOSITIONS, METHODS OF MAKING AND USING SAME

(57) Abstract

In accordance with the present invention, there are provided isolated nucleic acids encoding a human netrin, a human ATP binding cassette transporter, a human ribosomal L3 subtype, and a human augmienter of liver regeneration as well as isolated protein products encoded thereby. The present invention provides nucleic acid probes that hybridize to invention nucleic acids as well as isolated nucleic acids comprising unique gene sequences located on chromosome 16. Further provided are vectors containing invention nucleic acids, host cells transformed therewith, as well as transgenic non-human mammals that express invention polypeptides. The present invention includes antisense oligonucleotides, antibodies and compositions containing same. Additionally, the invention provides methods for identifying compounds that bind to invention polypeptides.



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NOVEL HUMAN CHROMOSOME 16 GENES, COMPOSITIONS, METHODS OF MAKING AND USING SAME

BACKGROUND OF THE INVENTION

The assembly of contiguous cloned genomic reagents is a necessary step in the process of disease-gene identification using a positional cloning approach. The rapid development of high density genetic maps based on polymorphic simple sequence repeats has facilitated contig assembly using sequence tagged site (STS) content mapping. Most contig construction efforts have relied on yeast artificial chromosomes (YACs), since their large insert size uses the current STS map density more advantageously than bacterial-hosted systems. This approach has been validated for multiple human chromosomes with YAC coverage ranging from 65-95% for many chromosomes and contigs of 11 to 36 Mb being described (Chumakov *et al.*, *Nature* 377 (Supp.):175-297, 1995; Doggett *et al.*, *Nature* 377 (Supp.):335-365, 1995b; Gemmill *et al.*, *Nature* 377 (Supp.):299-319, 1995; Krauter *et al.*, *Nature* 377 (Supp.):321-333, 1995; Shimizu *et al.*, *Cytogenet. Cell Genet.* 70:147-182, 1995; van-Heyningen *et al.*, *Cytogenet. Cell Genet.* 69:127-158, 1995).

Despite numerous successes, the YAC cloning system is not a panacea for cloning the entire genome of complex organisms due to intrinsic limitations that result in substantial proportions of chimeric clones (Green *et al.*, *Genomics* 11:658-669, 1991; Bellanne-Chantelot *et al.*, *Cell* 70:1059-1068, 1992; Nagaraja *et al.*, *Nuc. Acids Res.* 22:3406-3411, 1994), as well as clones that are rearranged, deleted or unstable (Neil *et al.*, *Nuc. Acids Res.* 18:1421-1428, 1990; Wada *et al.*, *Am. J. Hum. Genet.* 46:95-106, 1990; Zuo *et al.*, *Hum. Mol. Genet.* 1:149-159, 1992; Szepetowski *et al.*, *Cytogenet. Cell Genet.* 69:101-107,

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1995). At least some of these cloned artifacts are a product of the recombinational machinery of yeast acting on the various types of repetitive elements in mammalian DNA (Neil *et al., supra.* 1990; Green *et al., supra.* 1991; Schlessinger *et al., Genomics* 11:783-793, 1991; Ling *et al., Nuc. Acids Res.* 21:6045-6046, 1993; Kouprina *et al., Genomics* 21:7-17, 1994; Larionov *et al., Nuc. Acids Res.* 22:4154-4162, 1994).

Accordingly, alternative cloning systems must be used in concert with YAC-based approaches to complement localized YAC cloning deficiencies, to enhance the resolution of the physical map, and to provide a sequence-ready resource for genome-wide DNA sequencing. Several exon trapping methodologies and vectors have been described for the rapid and efficient isolation of coding regions from genomic DNA (Auch *et al., Nuc. Acids Res.* 18:6743-6744, 1990; Duyk *et al., Proc. Natl. Acad. Sci., USA* 87:8995-8999, 1990; Buckler *et al., Proc. Natl. Acad. Sci., USA* 88:4005-4009, 1991; Church *et al., Nature Genet.* 6:98-105, 1994). The major advantage of exon trapping is that the expression of cloned genomic DNAs (cosmid, P1 or YAC) is driven by a heterologous promoter in tissue culture cells. This allows for coding sequences to be identified without prior knowledge of their tissue distribution or developmental stage of expression. A second advantage of exon trapping is that exon trapping allows for the identification of coding sequences from only the cloned template of interest, which eliminates the risk of characterizing highly conserved transcripts from duplicated loci. This is not the case for either cDNA selection or direct library screening.

Exon trapping has been used successfully to identify transcribed sequences in the Huntington's disease locus (Ambrose *et al., Hum. Mol. Genet.* 1:697-703, 1992; Taylor *et al., Nature Genet.* 2:223-227, 1992; Duyao *et al., Hum. Mol. Genet.* 2:673-676, 1993) and BRCA1 locus (Brody *et al., Genomics* 25:238-247, 1995; Brown *et al., Proc. Natl.*

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Acad. Sci., USA 92:4362-4366, 1995). In addition, a number of disease-causing genes have been identified using exon trapping, including the genes for Huntington's disease (The Huntington's Disease Collaborative Research Group, *Cell* 72:971-983, 1993), neurofibromatosis type 2 (Trofatter *et al.*, *Cell* 72:791-800, 1993), Menkes disease (Vulpe *et al.*, *Nature Genet.* 3:7-13, 1993), Batten Disease (The International Batten Disease Consortium, *Cell* 82:949-957, 1995), and the gene responsible for the majority of Long-QT syndrome cases (Wang *et al.*, *Nature Genet.* 12:17-23, 1996).

A 700 kb CpG-rich region in band 16p13.3 has been shown to contain the disease gene for ~90% of the cases of autosomal dominant polycystic kidney disease (PKD1)(Germino *et al.*, *Genomics* 13:144-151, 1992; Somlo *et al.*, *Genomics* 13:152-158, 1992; The European Polycystic Kidney Disease Consortium, *Cell* 77:881-894, 1994) as well as the tuburin gene (TSC2), responsible for one form of tuberous sclerosis (The European Chromosome 16 Tuberous Sclerosis Consortium, *Cell* 75:1305-1315, 1993). An estimated 20 genes are present in this region of chromosome 16 (Germino *et al.*, *Kidney Int. Supp.* 39:S20-S25, 1993). Characterization of the region surrounding the PKD1 gene in 16p13.3, however, has been complicated by duplication of a portion of the genomic interval more proximally at 16p13.1 (The European Polycystic Kidney Disease Consortium, *supra.* 1994).

This chromosomal segment serves as a challenging test for large-insert cloning systems in *E. coli* and yeast since it resides in a GC-rich isochore (Saccone *et al.*, *Proc. Natl. Acad. Sci., USA* 89:4913-4917, 1992) with an abundance of CpG islands (Harris *et al.*, *Genomics* 7:195-206, 1990; Germino *et al.*, *supra.* 1992), genes (Germino *et al.*, *supra.* 1993) and Alu repetitive sequences (Korenberg *et al.*, *Cell* 53:391-400, 1988). Chromosome 16 also contains more low-copy repeats than other chromosomes with almost 25% of its cosmid contigs hybridizing to more than one chromosomal location when analyzed by fluorescence *in situ* hybridization (FISH) (Okumura *et al.*, *Cytogenet. Cell*

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Genet. 67:61-67, 1994). These types of repeats and sequence duplications interfere with "chromosome walking" techniques that are widely used for identification of genomic DNA and pose a challenge to hybridization-based methods of contig construction. This is because these techniques rely on hybridization to identify clones containing overlapping fragments of genomic DNA; thus, there is a high likelihood of "walking" into clones derived from homologues instead of clones derived from the authentic gene. In a similar manner, the sequence duplications and chromosome 16-specific repeats also interfere with the unambiguous determination of a complete cDNA sequence that encodes the corresponding protein. Furthermore, low copy repeats may lead to instability of this interval in bacteria, yeast and higher eukaryotes.

Thus, there is a need in the art for methods and compositions which enable accurate identification of genomic and cDNA sequences corresponding to authentic genes present on highly repetitive portions of chromosome 16, as well as genes similarly situated on other chromosomes. The present invention satisfies this need and provides related advantages as well.

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SUMMARY OF THE INVENTION

In accordance with the present invention, there are provided isolated nucleic acids encoding a human netrin, a human ATP binding cassette transporter, a human ribosomal L3 subtype, and a human augmenter of liver regeneration.

The present invention further provides isolated protein products encoded by a human netrin gene, a human ATP binding cassette transporter gene, a human ribosomal L3 gene, and a human augmenter of liver regeneration gene.

Additionally, the present invention provides nucleic acid probes that hybridize to invention nucleic acids as well as isolated nucleic acids comprising unique gene sequences located on chromosome 16.

Further provided are vectors containing invention nucleic acids as well as host cells transformed with invention vectors.

Transgenic non-human mammals that express invention polypeptides are provided by the present invention.

The present invention includes antisense oligonucleotides, antibodies and compositions containing same.

Additionally, the invention provides methods for identifying compounds that bind to invention polypeptides. Such compounds are useful for modulating the activity of invention polypeptides.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic diagram of the P1 contig and trapped exons.

Figures 2A and 2B show an alignment of selected exon traps with sequences in the databases.

Figures 3A through 3C show 6803 bp of hNET genomic sequence from P1 clone 53.8B (SEQ ID NO:19).

Figures 4A and 4B show 1743 bp of hNET cDNA and deduced amino acid sequence coding for a human homologue of chicken netrin genes (SEQ ID NOs:20 and 21).

Figures 4C and 4D show the nucleotide sequence of the 1.9 kb hNET cDNA including both 5' and 3' UTRs (SEQ ID NO:78).

Figure 5 shows an amino acid comparison between chicken netrin-1 (SEQ ID NO:22), chicken netrin-2 (SEQ ID NO:23) and hNET (SEQ ID NO:21). Shaded boxes denote regions of identical homology. The laminin domains V and VI and the C-terminal domain (C) are indicated by arrows with domain V divided into three sub-components (V-1 to V-3). The asterisks identify a motif for adhesion/signaling receptors.

Figure 6 shows a graphical representation of the homology between domains of chicken netrin-1, chicken netrin-2 and hNET.

Figure 7 shows exon traps, RT-PCR products and cDNA from the ABCgt.1 clone. Exon traps are shown above. ABCgt.1 DNA is shown below the exon traps with the position of the Genetrapper selection (S) and repair (R) oligonucleotides indicated. The position of the RT-PCR clones are shown below the cDNA.

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Figures 8A-8G show 5.8 kb of cDNA and deduced amino acid sequence encoding ABCgt.1 clone (SEQ ID NOs:24 and 25).

Figure 9A-9D show an amino acid alignment of murine ABC1 (SEQ ID NO:26) and ABC2 (SEQ ID NO:27) with clone ABCgt.1 (SEQ ID NO:25). Hyphens denote gaps; asterisks denote identical residues, while periods denote conservative substitutions. The location of the ATP binding cassettes is shown by the boxed regions. Numbers at the right show the relative position of the proteins.

Figure 10 shows the region of the transcriptional map of the PKD1 locus from which P1 clones 49.10D, 109.8C and 47.2H were isolated. The open boxes represent trapped exons with their relative position indicated below the RPL3L (SEM L3) gene. **c**, **r** and **h** identify the location of the capture, repair and hybridization oligonucleotides, respectively.

Figures 11A-11B show the nucleotide and deduced amino acid sequence of the SEM L3 cDNA, now designated RPL3L (SEQ ID NOs:28 and 29). The 5' upstream inframe stop codon is underlined and the arrows indicate the site of the polyA tract of the two shorter cDNA clones that were also isolated.

Figure 12 shows a comparison of the deduced amino acid sequences from human (SEQ ID NO:30), bovine (SEQ ID NO:31), murine (SEQ ID NO:32) and the RPL3L (SEM L3) (SEQ ID NO:29) genes. Dashes indicate sequence identity to the human L3 gene. The nuclear targeting sequence at the N-terminal end is shaded and the bipartite motif is boxed.

Figure 13 shows the nucleotide and deduced amino acid sequence of the hALR cDNA (SEQ ID NO:33 and 34).

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Figure 14 shows a comparison of the deduced amino acid sequences from rat ALR and human ALR (SEQ ID NOs:35 and 34), respectively.

Figures 15A-15J show the nucleotide and deduced amino acid sequence of full-length hABC3 cDNA (SEQ ID NOs:74 and 75).

Figure 16 shows a physical map of the region containing the hABC3 gene.

Figure 17A shows the deduced amino acid sequence for hABC3 (SEQ ID NO:75) aligned to the murine ABC1 (SEQ ID NO:26) and ABC2 (SEQ ID NO:27) sequences (Luciani *et al.*, *Genomics* 21:150-159, 1994) and sequence predicted to be encoded by *C. elegans* cosmid C.48B4.4 (SEQ ID NO:77) (Wilson *et al.*, *Nature* 368:32-38, 1994). Sequence identity is shown by letters, with mismatches denoted as periods. Gaps inserted during the alignment are also shown (=). For ABC1, ABC2 and C.48B4.4, only those sequences included in, and C-terminal to, the first ATP-binding domain are shown. Boxes denote the ATP binding cassettes (I and III) and the HH1 domain (II).

Figure 17B shows a schematic diagram of the ABC3 protein showing the transmembrane (TM) domains, ATP binding cassette (ABC) domains, Linker and HH1 domains.

Figure 18 shows a map of the genomic interval surrounding the human netrin gene.

Figure 19A shows a GRAIL2 analysis of coding sequences in the 6.8 kb genomic sequence from 53.8B P1.

Figure 19B shows the results of a Pustell DNA/protein matrix comparing genomic sequence to chicken netrin-2.

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Figure 20A shows alignment of the human netrin with chicken netrin-1, chicken netrin-2 and UNC-6 (SEQ ID NO: 79).

Figure 20B shows a schematic of the genomic sequence with boxes representing exons and lines denoting the introns. Untranslated region is shown in black, with the location of the start codon indicated by the arrow. The domain structure of the human netrin protein is shown below the gene structure. The position of introns in the *Drosophila* netrin genes is shown by arrows, with the non-conserved intron being denoted by the open arrow.

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DETAILED DESCRIPTION OF THE INVENTION

All patent applications, patents, and literature references cited in this specification are hereby incorporated by reference in their entirety. In case of conflict or inconsistency, the present description, including definitions, will control.

Definitions:

1. "complementary DNA (cDNA)" is defined herein as a single-stranded or double-stranded intronless DNA molecule that is derived from the authentic gene and whose sequence, or complement thereof, encodes a protein.

2. As referred to herein, a "contig" is a continuous stretch of DNA or DNA sequence, which may be represented by multiple, overlapping, clones or sequences.

3. As referred to herein, a "cosmid" is a DNA plasmid that can replicate in bacterial cells and that accommodates large DNA inserts from about 30 to about 51 kb in length.

4. The term "P1 clones" refers to genomic DNAs cloned into vectors based on the P1 phage replication mechanisms. These vectors generally accommodate inserts of about 70 to about 105 kb (Pierce *et al., Proc. Natl. Acad. Sci., USA*, 89:2056-2060, 1992).

5. As used herein, the term "exon trapping" refers to a method for isolating genomic DNA sequences that are flanked by donor and acceptor splice sites for RNA processing.

6. "Amplification" of DNA as used herein denotes a reaction that serves to increase the concentration of a particular DNA sequence within a mixture

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or DNA sequences. Amplification may be carried out using polymerase chain reaction (PCR) (Saiki *et al.*, *Science*, 239:487, 1988), ligase chain reaction (LCR), nucleic acid-specific based amplification (NSBA), or any method known in the art.

7. "RT-PCR" as used herein refers to coupled reverse transcription and polymerase chain reaction. This method of amplification uses an initial step in which a specific oligonucleotide, oligo dT, or a mixture of random primers is used to prime reverse transcription of RNA into single-stranded cDNA; this cDNA is then amplified using standard amplification techniques e.g. PCR.

A P1 contig containing approximately 700 kb of DNA surrounding the PKD1 and TSC2 gene was assembled from a set of 12 unique chromosome 16-derived P1 clones obtained by screening a 3 genome equivalent P1 library (Shepherd *et al.*, *Proc. Natl. Acad. Sci., USA* 91:2629-2633, 1994) with 15 distinct probes. Exon trapping was used to identify transcribed sequences from this region in 16p13.3.

96 novel exon traps have been obtained containing sequences from a minimum of eighteen genes in this interval. The eighteen identified genes include five previously reported genes from the interval and a previously characterized gene whose location was unknown (Table I). Additional exon traps have been mapped to genes based on their presence in cDNAs, RT-PCR products, or their hybridization to distinct mRNA species on Northern blots.

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TABLE I: Database Homologies

Gene[a]	Independent Exon Traps[b]	Clone[c]	Transcript Size	Database Homology[d]	Accession Number of Best Hit[e]	P value[f]
A	6	2 kb (cDNA)	8 kb	Probable protein kinase [*S. cerevisiae*]	Z48149	6.3e-83
B	1	1.3 kb (cDNA)	2.5	No Significant homology		
C	1	0.55 kb (Exon Trap) 0.6 kb (3' RACE)	1.4 kb	N-acetylglucosamine-6-phosphate deacetylase [*C. elegans*]	P34480	7.4e-73
D	2	Exon trap (159 bp) Exon trap (196 bp)	- -	Neurin-2 [*G. gallus*] Neurin-2 [*G. gallus*]	B54665 B54665	3.7e-11 6.1e-33
E	1	Exon trap (100 bp)	-	ABC1 gene product [*M. musculus*]	P41233	0.0047
F	3 2	1.1 kb (RT-PCR) 2.8 kb (cDNA)	7 kb 7 kb	ABC2 gene product [*M. musculus*] ABC1 gene product [*M. musculus*]	P41234 P41233	3.0e-28 7.1e-65
G	2	1.8 kb (cDNA)	2.5 kb	RNA-Binding protein [*Homo sapiens*]	L37368	2.6e-176
H	2	1.2 kb (RT-PCR)	2.5 kb	phi AP3 [*M. musculus*]	S41688	2.9e-169
I	1	0.45 kb (Exon Trap)	3.0 + 4.5 kb	No significant homologies		
J	2	0.24kb (RT-PCR)	2 kb	Rab26 [*R. norvegicus*]	U18771	3.6e-56
K	1	Exon trap (219 bp)	§	40S Ribosomal protein S4 [*Homo sapiens*]	P15880	7.3e-18
L	5	1.7 kb (cDNA)	1.6 kb	60s Ribosomal protein L3 [*Homo sapiens*]	S34195	6.7e-233
M	1	0.7 kb (cDNA)	1.3 kb	Hypothetical 17.2 Kd protein [*C. elegans*]	P34436	6.2e-10

a. Gene as denoted in Fig. 1.
b. Number of the trapped exon present in cloned cDNA or PCR product.
c. Size of clone with type of clone indicated in parentheses.
d. Significant homology in databases as determined by BLASTX.
e. Accession Number of best hit.
f. Smallest sum probability for the best database match.
- Northern analysis was not performed due to the small size of the exon traps.
§. Up to 200 copies of LLREP3 are present in the genome.

Exon trapping was performed using an improved trapping vector (Burn *et al.*, *Gene* 161:183-187, 1995), with the resulting exon traps being characterized by DNA sequence analysis. In order to determine the relative efficiency of the exon trapping procedure, exon traps were compared to the cDNA sequences for those genes known to be in the interval around the PKD1 gene (Figure 1). Single exon traps were obtained from the human homologue of the ERV1 (Lisowsky *et al.*, *Genomics* 29:690-697, 1995) and the ATP6C proton pump genes (Gillespie *et al.*, *Proc. Natl. Acad. Sci., USA* 88:4289-4293, 1991). The horizontal line at the top of Figure 1 shows the position of relevant DNA markers with the scale (in kilobases). The position of NotI sites is shown below the horizontal line. The position and orientation of the known genes is indicated by arrows with the number of exon traps obtained from each gene shown in parentheses. The position of the transcription units described in this report (A through M) are shown below the known genes. The Genbank Accession numbers of corresponding exon traps are shown below each transcriptional unit. P1 clones are indicated by the overlapping lines with the name of the clone shown above the line. The position of trapped exons which did not map to characterized transcripts are shown below the P1 contig. Vertical lines denote the interval within the P1 clone(s) detected by the exon traps in hybridization studies.

In contrast, eight individual exon traps were isolated from the TSC2 gene and ten from the CCNF gene (The European Chromosome 16 Tuberous Sclerosis Consortium, *supra*. 1993; Kraus *et al.*, *Genomics* 24:27-33, 1994). Trapped sequences from three of the exons present in the PKD1 gene were obtained (The American PKD1 Consortium, *Hum. Mol. Genet.* 4:575-582, 1995; The International Polycystic Kidney Disease Consortium, *Cell* 81:289-298, 1995; Hughes *et al.*, *Nature Genet.* 10:151-160, 1995). 16 additional exon traps from the 109.8C and 47.2H P1 clones were also obtained.

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Sequences present in two exon traps (Genbank Accession Nos. L75926 and L75927), localizing to the region of overlap between the 96.4B and 64.12C P1 clones, were shown to contain sequences from the previously described human homologue to the murine RNPS1 gene (Genbank Accession No. L37368), encoding an S phase-prevalent DNA/RNA-binding protein (Schmidt *et al.*, *Biochim. Biophys. Acta* 1216:317-320, 1993). A comparison of these exon traps to the dbEST database indicated that they were also contained in cDNA 52161 from the I.M.A.G.E. Consortium (Lennon *et al.*, *Genomics* 33:151-152, 1996). Based on these data, the hRNPS1 gene can be mapped to 16p13.3 near DNA marker D16S291 (transcript G in Figure 1).

Two exon traps from the 1.8F P1 clone were found to have a high level of homology to the previously described murine ΦAP3 encoding a zinc finger-containing transcription factor (Fognani *et al.*, *EMBO J.* 12:4985-4992, 1993). The mΦAP3 protein, a zinc finger-containing transcription factor, is believed to function as a negative regulator for genes encoding proteins responsible for the inhibition of cell cycling (Fognani *et al.*, *supra.*). The two exon traps were linked by PCR, with the resulting 1.2 kb PCR product being 85% identical at the nucleotide level to the murine ΦAP3 cDNA. Hybridization of the ΦAP3-like exon traps to the dot blotted P1 contig indicated that the gene lies in the non-overlapping region of the 1.8F P1, between the DNA markers KLH7 and GGG12 (transcript H in Figure 1).

Significant homology was also seen between two exon traps obtained from the 97.10G P1 and the rat Rab26 gene encoding a *ras*-related GTP-binding protein involved in the regulation of vesicular transport (Nuoffer *et al*, *Ann. Rev. Biochem.* 63:949-990, 1994; Wagner *et al.*, *Biochem. Biophys. Res. Comm.* 207:950-956, 1995). The Rab26-like exon traps were linked by RT-PCR (transcript J in Figure 1).

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with the encoded sequences being 94% (83/88) identical at the protein level to Rab26. See, for example, Figure 2 showing an alignment of the following selected exon traps with sequences in the databases. An alignment of sequences encoded by exon trap L48741 (SEQ ID NO:1) and N-acetylglucosamine-6-phosphate deacetylase from *C. Elegans* (SEQ ID NO:2), *E. coli* (SEQ ID NO:3) and *Haemophilus* (SEQ ID NO:4). The EGF repeat from netrin-1 (SEQ ID NO:7), netrin-2 (SEQ ID NO:6) and UNC-6 (SEQ ID NO:8) are shown aligned to one of the translated netrin-like exon traps (Genbank Accession No. L75917) (SEQ ID NO:5). An alignment of sequences from the second netrin-like exon trap (Genbank Accession No. L75916) (SEQ ID NO:9) and netrin-1 (SEQ ID NO:11) and netrin-2 (SEQ ID NO:10) is shown. An alignment of the translated Rab26-like RT-PCR product (Genbank Accession Nos. L48770-L48771) (SEQ ID NO:12) and rat Rab26 (SEQ ID NO:13). Sequences encoded by exon trap L48792 (SEQ ID NO:14) are shown aligned to sequences from the pilB transcriptional repressor from *Neisseria gonorrhoeae* (SEQ ID NO:15), sequences predicted by computer analysis to be encoded by cosmid F44E2.6 from *C. elegans* (SEQ ID NO:17), the YCL33C gene product from yeast (Genbank Accession No. P25566) (SEQ ID NO:16), and a transcriptional repressor from *Haemophilus* (SEQ ID NO:18). Periods denote positions where gaps were inserted in the protein sequence in order to maintain alignment.

In order to correlate exon traps with individual transcripts, cDNA library screening and PCR based approaches were used to clone transcribed sequences containing selected exon traps. RT-PCR was used to link individual exon traps together in cases where the two exon traps had homology to similar sequences in the databases. In cases where only single exon traps were available, 3' RACE or cDNA library screening was used to obtain additional sequences. Sequences from the exon traps and cloned products were used to map the position, and when possible the orientation, of the corresponding transcription units.

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Six unique exon traps, containing sequences from at least eight exons, were shown to be from a transcriptional unit in the centromeric most P1 clone, 94.10H (transcript A in Figure 1). A 2 kb cDNA linking the six exon traps was isolated and shown to hybridize to an 8 kb transcript. Additional hybridization studies indicated that the gene was oriented centromeric to telomeric, with at least 6 kb of the transcript originating from sequences centromeric of the P1 contig. Extensive homology was observed between the translated cDNA and a variety of protein kinases; however, the presence of the conserved HRDLKPEN motif (SEQ ID NO:71) encoded in exon trap L48734, as well as the partial cDNA, suggests that it encodes a serine/threonine kinase (van-der-Geer *et al.*, *Ann. Rev. Cell Bio.* 10:251-337, 1994).

cDNAs were isolated using sequences derived from a separate 94.10H exon trap (Genbank Accession No. L48738) and the position and orientation of the corresponding transcription unit were determined. Two cDNA species were obtained using exon trap L48738 as a probe, with the only homology between the two species arising from the 109 bases contained in the exon trap. Using oligonucleotide probes, the transcription unit was mapped to a position near the 26-6DIS DNA marker, in a telomeric to centromeric orientation; however, only one of the cDNA species mapped to the P1 contig (transcript B in Figure 1). Based on these data, it is likely that the second cDNA species originated from a region outside of the P1 contig, possibly from the duplicated 26-6PROX marker located further centromeric in 16p13.3 (Gillespie *et al.*, *Nuc. Acids Res.* 18:7071-7075, 1990).

The 110.1F P1 clone contains at least two genes in addition to the ATP6C gene. Using BLASTX to search the protein databases, significant homology was observed between sequences encoded by exon trap L48741 and the N-acetylglucosamine-6-phosphate deacetylase (nagA) proteins

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from *C. elegans* (Wilson *et al.*, *supra*. 1994), *E. coli* (Plumbridge, *Mol. Microbiol.* 3:505-515, 1989) and *Haemophilus* (Fleischmann *et al.*, *Science* 269:496-512, 1995). An alignment of the nagA proteins to the translated exon trap revealed the presence of multiple conserved regions (Figure 2), suggesting that the exon trap contains sequences from the human nagA gene. Additional sequences from the nagA-like transcript have been cloned using 3' RACE and the transcription unit mapped to a region between NotI sites 2 and 3 in Figure 1. The gene is oriented telomeric to centromeric with NotI site 2 being present in the 3' UTR of the RACE clone (transcript C in Figure 1).

Two additional exon traps (Genbank Accession Nos. L75916 and L75917), mapping to the region of overlap between the 110.1F and 53.8B P1 clones (transcript D in Figure 1), were shown to have homology with the chicken netrins (Kennedy *et al.*, *Cell* 78:425-435, 1994; Serafini *et al.*, *Cell* 78:409-424, 1994) and the *C. elegans* UNC-6 protein (Ishii *et al.*, *Neuron* 9:873-881, 1992)(Figures 2 and 20A).

Sequences encoded by exon trap, L75917, were shown to have significant homology with the C-terminal most epidermal growth factor (EGF) repeat found in the netrin- and UNC-6 proteins (Figures 2 and 20A). Exon trap L75917 encodes sequences which are 98% identical to sequences from the third epidermal growth factor (EGF) repeat of chicken netrin-2 and 90% identical to sequences from the same region of netrin-1. The netrin-like trap, L75916, encodes sequences from the more divergent C-terminal domain of the netrins which are 43% identical to sequences contained in the C-terminal domain of netrin-1 and netrin-2 (Figures 2 and 20A). This region is the least conserved between UNC-6 and the netrins, with sequences being 63% conserved between netrin-1 and netrin-2 and 29% conserved between netrin-2 and UNC-6 (Serafini *et al.*, *supra*.).

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The netrins define a family of chemotropic factors which have been shown to play a central role in axon guidance. Axonal growth cones are guided to their target by both local cues, present in the extracellular matrix or on the surface of cells, and long-range cues in the form of diffusible chemoattractants and chemorepellents (Goodman and Shatz, *Cell* 72:77-98, 1993; Keynes and Cook, *Curr. Opin. Neurobiol.* 5:75-82, 1995).

Chicken netrin-1 and netrin-2 have been shown to function as chemoattractants for developing spinal commissural axons (Serafini *et al.*, *Cell* 78:409-424, 1994; Kennedy *et al.*, *Cell* 78:425-435, 1994) with netrin-1 also acting as a chemorepellant for trochlear motor axons (Colamarino and Tessier-Lavigne, *Cell* 81:621-629, 1995). Comparative analysis revealed the presence of extensive homology between the chicken netrins and *C. elegans* UNC-6 protein which is required for circumferential cell migration and axon guidance (Hedgecock *et al.*, *Neuron* 4:61-85, 1990; Ishii *et al.*, *Neuron* 9:873-881, 1992). More recently, two *Drosophila* netrins, NETA and NETB, have been described and shown to be required for commissural axon guidance as well as for guidance of motor neurons to their target muscles (Harris *et al.*, *Cell* 17:217-228, 1996; Mitchell *et al.*, *Cell* 17:203-215, 1996). These studies indicate that the netrin family of chemoattractant and chemorepellant proteins is conserved between invertebrates and vertebrates.

The genomic interval containing the netrin-like exon traps was sequenced in order to obtain additional sequence information from the gene and to rule out the possibility that the exon traps were derived from a pseudogene. In preliminary studies using the 53.8B genomic P1 clone, the netrin-like exon traps were mapped to a 6 kb *Xho*I fragment. See, for example, Figure 18 wherein relevant DNA markers are shown on top of the horizontal line, with *Not*I sites (N) being shown below the line. The location and orientation of the ATP6C, CCNF, and nagA

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transcriptional units have been previously described (Gillespie *et al.*, *Proc. Natl. Acad. Sci., USA* 88: 4289-4293, 1991; Kraus *et al.*, *Genomics* 24: 27-33, 1994; Burn *et al.*, *Genome Research* 6: 525-537, 1996) and are shown below the genomic interval. The two P1 clones containing the netrin gene are shown below the schematic diagram of the interval. The location of the 6.8 kb of genomic sequence is enlarged below the P1 clones. The position of the two exon traps in the 6.8 kb of genomic sequence is also indicated.

The 6 kb fragment, and the adjacent 3.5 kb *XhoI* fragment, were subcloned and used to screen a random shotgun library from the 53.8B P1 clone. Subclones which were positive by hybridization were sequenced with forward and reverse vector primers. A total of 88 subclones were sequenced in this manner.

Additional sequence was obtained using internal primers as well as end sequence from the parental *XhoI* fragments. A total of 6.8 kb of genomic sequence with an overall redundancy of 7-fold was sequenced. The GC-content for the sequenced region was found to be 68.9%, which is slightly higher than the 62.8% observed for the 53 kb of genomic sequence from the PKD1 gene, located 350 kb further telomeric (The American PKD1 Consortium, 1995, *supra*; Burn *et al.*, 1996, *supra*).

Computer analyses were performed to identify putative exons. GRAIL2 analysis predicted six exons within the 6.8 kb of genomic sequence with database analysis indicating that all but one exon (exon 1), encoded sequences with homology to the chicken netrins. Figure 19A shows a GRAIL2 analysis of coding sequences in the 6.8 kb of genomic sequence from the 53.8B P1, with the gray scale denoting GC-content (white to light gray is GC rich and gray to black is AT rich), vertical boxes indicating relative quality of the predicted exons. A graphical

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depiction of the predicted exons is shown above the vertical boxes with light colored boxes denoting exons with a score of "excellent" (>80% probability) and dark colored boxes denoting exons with a score of "good" (>60% probability). The position of exon traps L75917 and L75916 (left to right, respectively) are shown above the GRAIL2 predicted exons. The structure of the gene based on comparison of the RT-PCR products and genomic sequence is shown at the top, the position of the exons in the genomic sequence is shown by the numbers above the exons. The 5' and 3' untranslated regions are also shown.

Additionally, the 6.8 kb of genomic sequence was compared to the protein sequences of the chicken netrins using a Pustell DNA/protein matrix. The genomic sequence (translated in all six frames) was compared to chicken netrin-2 in Figure 19B, using a PAM250 matrix with the minimum homology set at 50% and the window set at 20. Regions of homology are shown by heavy diagonal lines. Five exons were predicted by this analysis, with only the first GRAIL2 predicted exon not appearing to be *bona fide*. Sequences from the two exon traps were also predicted by GRAIL2; however, there were noteworthy differences (*cf* Figure 19A). In predicting sequences present in exon trap L75917, GRAIL2 included an additional 55 bp at the 5' end of the exon. The first of the two exons present in exon trap L75916 was not predicted by GRAIL2, while GRAIL2 added additional bases to the 5' and 3' ends of the second exon present in this exon trap.

A search of the Expressed Sequence Tags (EST) database did not reveal the presence of any ESTs from the human netrin gene. Nor was the human netrin message detected by Northern and/or RNA dot blot analysis using mRNA from over fifty different adult and fetal tissues, suggesting that hNET has an extremely restricted pattern of expression and when expressed is present in low abundance. Two murine ESTs, however, were identified from a brain library and a whole fetus library (Genbank Accession Nos.

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W59766 and AA048205, respectively) which have significant homology to hNET. The murine ESTs contain overlapping sequence with a total of 477 bp of contiguous sequence being represented. This 477 bp contiguous sequence aligns to the 5' end of the human netrin cDNA and includes 47 bp of 5' UTR and sequences encoding the N-terminal 143 amino acids. A comparison of the deduced human and murine protein sequence indicated that the two proteins were 89.5% (128/143) identical.

Characterization of the Human Netrin Transcript

In order to confirm the structure of the netrin gene, RT-PCR was performed using primers designed from the predicted exons. Since the predicted human netrin appeared to slightly more homologous to netrin-2 than netrin-1 (57% versus 54%, respectively) and netrin-2 is expressed in the spinal cord of chicken, adult human spinal cord polyA+ RNA was utilized as a template. RT-PCR products were obtained with only a portion of the primer pairs; however, even this required the use of nested primers and two rounds of PCR, with low yields making it necessary to use hybridization and radiolabeled probes to visualize the products. The low yield, and lack of RT-PCR products in some cases, was attributed to the high GC-content of the products (70-80%). The addition of betaine to a final concentration of 2.5 M in the PCR reactions was found to dramatically improve yield and purity of the RT-PCR products. (International Publication No. WO 96/12041; Reeves *et al.* (1994) *Am. J. Hum. Genet.* 55:A238; Baskaran *et al.* (1996) *Genome Research* 6:633-638).

Assembly of the RT-PCR products revealed a 1743 bp open reading frame (ORF) with an in-frame stop codon upstream of the proposed start methionine. In verifying the start and stop codons, a 209 bp 5' UTR and a 22 bp 3' UTR were cloned. Additional sequences from the respective UTRs were not cloned, however, since the goal of the RT-PCR experiments was to only confirm the predicted protein

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sequence and not to assemble a full-length cDNA. The position of the intron-exon boundaries was determined based on the comparison of the genomic sequence and the RT-PCR clones (Figure 19A).

A 1.9 kb cDNA, hNET, was cloned by performing nested PCR using spinal cord cDNA as template and standard PCR conditions with the addition of betaine. The human netrin protein is predicted to be 580 amino acids in size, with the common domain structure of the netrin family being conserved. In Figure 20A positions where the chicken netrins and UNC-6 sequences match the human sequence are denoted by periods while gaps introduced during the alignment are shown by hyphens. Arrows above the sequence alignment show the boundaries of the laminin VI and V domains, and C-terminal region (C) as described (Serafini *et al.*, *Cell* 78: 409-424, 1994). The signal sequence (S) is also shown. V-1, V-2, and V-3 designate each of the EGF domains that constitute domain V.
The hNET coding sequence and its predicted protein product are shown in Figures 4A and 4B. Figures 4C and 4D show full length hNET cDNA including both 5' and 3' UTR sequence.

Several lines of evidence rule against the possibility that the human netrin gene described herein represents a pseudogene. First, none of the exons in the coding region contain stop codons. Secondly, the overall gene structure described is highly conserved when compared to other members of the netrin/UNC-6 family. Third, despite the lack of signal in the Northern and RNA blot analysis, a mature transcript was isolated by RT-PCR. Finally, sequences in the murine EST database have been identified which are highly conserved. Taken together, these data indicate that a novel human netrin gene with a restricted pattern of expression has been identified.

Human netrins may have a significant role in neural regeneration. Though netrins do not by themselves

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promote axon growth, they do play a role in the orientation of axon growth. The combination of growth promoting activities with axon guidance cues would be a necessary requisite for directed neural regeneration.

The ability to clone a gene with such a restricted pattern of expression points out one of the strengths of the exon trapping procedure, since it is unlikely that the netrin gene would have been identified using cDNA selection or direct library screening. These results highlight the need for using a variety of approaches to identify and clone sequences from a large genomic contig.

Exon trapping results further show that there is a novel ATP Binding Cassette (ABC) transporter in the PKD1 locus located between the LCN1 and D16S291 markers in a centromeric to telomeric orientation. Database searches with the exon trap sequences show homology to the murine ABC1 and ABC2 genes (Luciani *et al., supra.* 1994). The human homologs of murine ABC1 and ABC2 have been cloned and mapped to human chromosome 9 (Luciani *et al. supra.* 1994). Sequences derived from the trapped exons along with those from cDNA selection and SAmple SEquencing (SASE) were used to recover overlapping partial cDNA clones.

Seven exon traps with homology to ABC transporters were isolated from P1 clones 30.1F, 64.12C and 96.4B. Additional sequences encoded by the ABC3 gene were obtained by RT-PCR (placenta and brain RNA as template) and library PCR (using commercially available lung cDNA library as template) using custom primers designed from the exon traps (Tables II and III). Three exon traps (L48758, L48759 and L48760) were obtained from the region of overlap between the 30.1F, 64.12C and 96.4B P1 clones (transcript F Figure 1), while a fourth exon (L48753) maps to the 79.2A P1 clone, exclusively (transcript E in Figure 1).

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TABLE II: Oligonucleotides Used to Clone Additional Sequences

Gene[a]	Method[b]	SEQ ID NO:	Oligonucleotide1[c]	SEQ ID NO:	Oligonucleotide 2[d]	clone size[e]
A	Genetrapper	36	TGACGCCGTGCCCATCCAGT	37	CAGCGTGGTGTTATGTTCCT	2.0 kb
B	Genetrapper	38	TTGGGCCTGTGCTGAACTAC	39	CGGCAAGCTGGTGATTAACA	1.3 kb
C	3'RACE	40	CGGCAGAGGATGCTGTGT	41	GCGGAGCCACCTTCATCA	0.6 kb
F	RT-PCR	42	GACGCTGGTGAAGGAGC	43	TCGCTGACCGCCAGGAT	1.1kb
H	RT-PCR	44	CTGTCGGGAAGGTCTCACTG	45	GTTCACCGCCTTGGAGGATT	1.1kb
J	RT-PCR	46	GTGTGGGGAAGACCTGTCTG	47	AGGAGGCCTTGTTGGTGACA	0.24kb
L	Genetrapper	48	ACGGACACCTGGGCTTC	49	AAACGGGAGGAGGTGGA	1.7kb
M	Genetrapper	50	TGTGGCTATGAGCTGTTCTC	51	GCAGTCCCGATTCTGAATAT	0.7 kb

a. Gene as denoted in Figure 1.
b. Method used to clone additional sequences. Lifetechnologies Genetrapper system, 3'RACE and RT-PCR.
c. Sequence of oligonucleotides used to obtain additional sequences. For the Genetrapper system, this oligonucleotide was used in the direct selection step. In the case of 3'RACE experiments, this oligonucleotide was the external prime. In the case of RT-PCR experiments, the designated oligonucleotide was used as a sense primer.
d. Sequence of oligonucleotides. In the Genetrapper experiments, this oligonucleotide was used in the repair step. For 3'RACE experiments, this was the internal primer. For RT-PCR experiments, this was the anitsense primer.
e. Size of clone obtained using the primer pair.

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TABLE IIIa: Oligonucleotides Used to Clone Additional Sequences from human ABC3

Method[a]	SEQ ID NO:	Oligonucleotide 1[b]	SEQ ID NO:	Oligonucleotide 2[c]	clone name[d]	clone size[e]
Genetrapper	52	CATTGCCCGTGCTGTCGTG	53	CATCGCCGCCTCCTTCATG	ABC3 (gt.1)	5.8 kb
RT-PCR	52	CATTGCCCGTGCTGTCGTG	54	GCGGAGCCACCTTCATCA	ABC3 (A12)	1.7 kb
RT-PCR	55	GACGCTGGTGAAGGAGC	56	ATCCTGGCGGTCAGCGA	ABC3 (3-12)	1.1 kb
RT-PCR	57	AGGGATTCGACATTGCC	58	CTTCAGAGACTCAGGGGCAT	ABC3 (#2)	0.5 kb

a. Method used to clone additional sequences. Lifetechnologies Genetrapper system and RT-PCR.
b. Sequence of oligonucleotides used to obtain additional sequences. For the Genetrapper system, this oligonucleotide was used in the direct selection step. In the case of RT-PCR experiments, the designated oligonucleotide was used as a sense primer.
c. Sequence of oligonucleotides. In the Genetrapper experiments, this oligonucleotide was used in the repair step. For RT-PCR experiments, this was the anitsense primer.
d. Assigned name of the isolated clone.
e. Size of clone obtained using the primer pair.

TABLE IIIb: Oligonucleotides Used to Clone Additional Sequences from human ABC3

5' clone[a]	SEQ ID NO:	5' primer[b]	3' clone[c]	SEQ ID NO:	3' primer[d]	clone name[e]	clone size[f]
et L48757	52	CATTGCCCGTGCTGTCGTG	et L48758	54	GCGGAGCCACCTTCATCA	ABC3 (A12)	1.7 kb
et L48758	55	GACGCTGGTGAAGGAGC	et L48760	56	ATCCTGGCGGTCAGCGA	ABC3 (3-12)	1.1 kb
et L48760	57	AGGGATTCGACATTGCC	et L75924	58	CTTCAGAGACTCAGGGGCAT	ABC3 (#2)	0.5 kb
sel. cDNA/SASE	76	AGCTGGCGCTCCTCCTCT	et L48757	53	CATCGCCGCCTCCTTCATG	ABC3 (#5)	0.9 kb

a. Clone used to derive the 5' primer.
b. Sequence of the sense primer used in the RT-PCR reaction.
c. Clone used to derive the 3' primer.
d. Sequence of the antisense primer used in the RT-PCR reaction.
e. Assigned name of the isolated clone.
f. Size of clone obtained using the primer pair.

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TABLE IV: Oligonucleotides Used to Clone Sequences from the human Netrin

Method[a]	SEQ ID NO:	Oligonucleotide 1[b]	SEQ ID NO:	Oligonucleotide 2[c]	clone named	clone size[e]
1° RT-PCR	59	GCCTGTCATCGCTCTAG	60	CAGTCGCAGGCCCTGCA		
2° PCR	61	GAGGACGCGCCAACATC	62	CGGCAGTAGTGGCAGTG	1121-1123	1264bp
1° RT-PCR	63	CCTGCCTCGCTTGCTCCTGC	64	CGGGCAGCCGCAGGCCGCAT		
2° PCR	65	CCTGCAACGGCCATGCCCGC	66	GCATCCCCGGCGGGCACCCA	1131-1141	601bp
1° RT-PCR	80	CTTGCAGGGCCTGCGAC	81	GAAGGCACAGGGTGAAC		
2° PCR	82	CTGCAACCAGACCACAG	83	TAGATGTGGGAGCAGCG	1125-1127	629 bp

a. Method used to clone sequences. For 2° PCR, the 1° RT-PCR product was diluted to a final concentration of one to one thousand.
b. Sequence of sense-strand oligonucleotides.
c. Sequence of antisense-strand oligonucleotides
d. Assigned name of the isolated cDNA clones.
e. Size of clone obtained using the primer pair.

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Exon traps from the hABC3 transporter encoded by transcript F encode sequences with homology to the R-domain of the murine ABC1 and ABC2 genes. The R-domain is believed to play a regulatory role based on the comparison to a conserved region in CFTR. To date, only ABC1, ABC2 and CFTR have been shown to contain an R-domain (Luciani *et al., supra.* 1994).

Additionally, a 1.1 kb RT-PCR product which links the three exon traps from transcript F, with the RT-PCR product detecting a 7 kb message on Northern blots has been obtained. Based on a search of the dbEST database, a cDNA from this region was obtained with sequences from exon traps L75924 and L75925 being contained in cDNA 49233 from the I.M.A.G.E. Consortium (Lennon *et al., supra.*). The presence of both cloned reagents in the same transcription unit has been confirmed using RT-PCR.

The ATP binding cassette (ABC) transporters, or traffic ATPs, comprise a family of more than 100 proteins responsible for the transport of a wide variety of substrates across cell membranes in both prokaryotic and eukaryotic cells (Higgins, C. F., *Annu. Rev. Cell. Biol.* 8:67-113, 1992; Higgins, C. F. *Cell* 82:693-696, 1995). Proteins belonging to the ABC transporter superfamily are linked by strong structural similarities. Typically ABC transporters have four conserved domains, two hydrophobic domains which may impart substrate specificity (Payne *et al., Mol. Gen. Genet.* 200:493-496, 1985; Foote *et al., Nature* 345:255-258, 1990; Anderson *et al., Science* 253:202-205, 1991; Shustik *et al., Br. J. Haematol.* 79:50-56, 1991; Covitz *et al., EMBO J.* 13:1752-1759, 1994), and two highly conserved domains associated with ATP binding and hydrolysis (Higgins, *supra.* 1992). ABC transporters govern unidirectional transport of molecules into or out of cells and across subcellular membranes (Higgins, *supra.* 1992). Their substrates range from heavy metals (Ouellette *et al., Res. Microbiol.* 142:737-746 1991) to peptides and full size proteins (Gartner *et al., Nature Genet.* 1:16-23 1992).

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In eukaryotic cells, ABC transporters exist either as single large symmetrical proteins containing all four domains or as dimers resulting from the association of two smaller polypeptides each containing a hydrophobic and ATP-binding domain. Examples of this multimeric structural form are human TAP proteins (Kelly *et al.*, *Nature* 355:641-644 1992) and the functional PMP70 protein (Kamijo *et al.*, *J. Biol. Chem.* 265:4534-40 1990). This multimeric structure is also found in numerous prokaryotic ABC transporters. The hydrophobic regions are comprised of up to six transmembrane spanning segments. Each ATP binding domain operates independently and may or may not be functionally equivalent (Kerem *et al.*, *Science* 245:1073-80 1989; Mimmack *et al.*, *Proc. Natl. Acad. Sci., USA* 86:8257-61 1989; Cutting *et al.*, *Nature* 346:366-369 1990; Kerppola *et al.*, *J. Biol. Chem.* 266:9857-65 1991).

Several of the ABC transporters thus far identified in humans have been shown to be clinically important. For example, overexpression of P-glycoproteins is responsible for multi-drug resistance in tumors (Gottesman *et al.*, *Ann. Rev. Biochem.* 62:385-427 1993). Classical cystic fibrosis (CF) as well as a large proportion of cases of bilateral congenital disease of the vas deferens (CBAVD) are caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), an ABC transporter (Kerem *et al.*, *supra.*; Cutting *et al.*, *supra.*). Defects in ABC transporters have also been implicated in Zellweger syndrome (Gartner *et al.*, *supra.*), and adrenoleukodystrophy (Mosser *et al.*, *Nature* 361:726-730 1993).

Two members of a novel ABC transporter subgroup (murine ABC1 and ABC2) have been shown to contain domains similar to the regulatory R-domain of CFTR (Luciani *et al.*, *supra.* 1994). Functionally, the mouse ABC1 protein has been shown to play a role in macrophage engulfment of apoptotic cells (Luciani *et al.*, *EMBO J.* 16:226-235, 1996),

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while the function of ABC2 remains unknown. All three proteins contain a large charged region containing several potential phosphorylation sites (Kerem *et al.*, *supra.*; Luciani *et al.*, *supra.* 1994). The charged amino acid residues within this region are sequentially arranged in blocks of alternating positive and negative charge.

A common feature of these particular ABC transporters, including hABC3, is the presence of a large linker domain between the two ATP binding cassettes. The presence of numerous polar residues and potential phosphorylation sites in the linker domain suggest that this region may play a regulatory role perhaps similar to that of the R-domain of CFTR (Kerem *et al.*, *supra.*). In addition, the four proteins also contain a hydrophobic region, the HH1 domain (Luciani *et al.*, *supra.* 1994), within the conserved linker domain. Although there is little homology at the sequence level between the HH1 domains of hABC3 and the murine ABCs, they appear to be structurally conserved with each domain predicted to have ß-sheet conformation. The similarity between these proteins would suggest that they all belong to the same ABC subfamily, originally defined by ABC1 and ABC2 (Luciani *et al.*, *supra.* 1994). The genes encoding the human homologues of ABC1 and ABC2 have been mapped to human chromosome 9 at q22-q31 and q34, respectively (Luciani *et al.*, *supra.* 1994).

Despite being members of the same subfamily, it is likely that ABC1, ABC2 and hABC3 have different functional roles. The differences present in the transmembrane and linker domains of ABC1, ABC2 and hABC3 may confer each with a unique substrate specificity. For example, alterations and mutations in the transmembrane domains of both prokaryotic and eukaryotic ABC transporters have been shown to alter substrate specificity (Payne *et al.*, *supra.*; Foote *et al.*, *supra.*; Covitz *et al.*, *supra.*) while changes to the R-domain of CFTR have been shown to alter its ion selectivity (Anderson *et al.*, *supra.*; Rich *et*

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al., *Science* 253:205-207 1991). The differences in the expression patterns of ABC1, ABC2 and hABC3 also suggest that the proteins may be functionally distinct. Murine ABC1 and ABC2 have been shown to be expressed at varying levels in a wide variety of adult and embryonic tissues, with the highest levels of ABC1 expression being seen in pregnant uterus and regions rich in monocytic cells while highest levels of ABC2 expression were seen in brain (Luciani *et al.*, *supra*. 1994; Luciani *et al.*, *supra*. 1996). In contrast, hABC3 is preferentially expressed in lung with significantly lower levels of expression being seen in brain, heart, and pancreas.

Apart from the structural differences between ABC1, ABC2 and hABC3, it is always possible that the three proteins play similar functional roles in different cell populations. To date, no function has been proposed for murine ABC2. However, recent data indicate that ABC1 is required for the engulfment of cells undergoing apoptosis, though the molecular mechanism underlying ABC1 function is unknown (Luciani *et al.*, *supra*. 1996). If hABC3 functions in a manner similar to ABC1, it could be expressed by pulmonary macrophages involved in host defense.

ABC transporters have been described for substrates ranging from small ions to large polysaccharides and proteins. Based on the high level of expression in lung, the substrate for hABC3 may play an integral role in the lung function, including ion or polysaccharide transport. Further clues may be provided by a closer examination of hABC3 expression in the lung. These studies would include the identification of the lung cells responsible for hABC3 expression as well as determining the subcellular localization of hABC3. The identification and cloning of the hABC3 cDNA may have implications for cystic fibrosis, since it contains a potential R-domain and is expressed at highest levels in the lung. If hABC3 does play an integral role in lung function, then modulation or

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alteration of hABC3 substrate specificity could have significant therapeutic implications for CF.

Several cDNAs were cloned using the GeneTrapper direct selection system and oligos designed from the 5' most trapped exon encoding sequences with homology to ABC1 (trapped exon L48747). The longest clone isolated with the GeneTrapper system from a normal human lung cDNA library using custom oligonucleotides designed from the 5' most exon trap was 5719 bp in length (ABCgt.1). An additional cDNA clone (ABC.5) was isolated using a radiolabeled 1.1 kb RT-PCR product (ABC3-12) as a probe (Figure 15). The 5' end of the ABC3 cDNA was further characterized using 5' RACE, with several RACE products containing multiple in-frame stop codons upstream of the start methionine.

Accordingly, the present invention provides a novel human ABC gene which has homology to the murine ABC1 and ABC2 genes, as well as sequences predicted to be encoded by cosmid C48B4.4 from *C. elegans* (Wilson *et al.*, *supra.*). A 6.4 kb cDNA has been assembled for the hABC3 transporter. The assembled cDNA contains a 5116 nucleotide long open reading frame encoding 1705 amino acids, with the predicted protein having a molecular weight of 191 kDa. The proposed start methionine is 50 bp upstream of the 5' end of clone ABCgt.1.

Five trapped exons from P1 clones 109.8C and 47.2H were shown to contain sequences with homology to the human ribosomal protein L3 cDNA, with hybridization studies indicating that the L3-like gene is oriented centromeric to telomeric (transcript L in Figure 1). The ribosomal L3 gene product is one of five essential proteins for peptidyltransferase activity in the large ribosomal subunit (Schulze and Nierhaus, *EMBO J.* 1:609-613, 1982). Not surprisingly, the L3 amino acid sequence is highly conserved across species. Mammalian L3 genes showing ~98% protein sequence identity have been characterized from man (Genbank Accession No. X73460), mouse (Peckham *et al.*,

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Genes Dev. 3:2062-2071, 1989), rat (Kuwano and Wool, *Biochem. Biophys. Res. Comm.* 187:58-64, 1992) and cow (Simonic *et al.*, *Biochim. Biophys. Acta* 1219:706-710, 1994). The cumulative percent identity between the trapped exons and the reported human ribosomal protein L3 cDNA was 74% (537/724) at the nucleotide level.

A full-length cDNA encoding a novel ribosomal L3 protein subtype, SEM L3, was isolated and sequenced (Figure 11). This gene is now designated RPL3L and has been assigned GenBank Accession No. U65581. The deduced protein sequence is 407 amino acids long and shows 77% identity to other known mammalian L3 proteins, which are themselves highly conserved. Hybridization analysis of human genomic DNA suggests this novel gene is single copy and has a tissue specific pattern of expression.

The expression pattern of the previously identified human L3 gene and the novel human RPL3L was determined using multiple tissue Northern blots. The human L3 gene showed a ubiquitous pattern of expression in all tissues with the highest expression in the pancreas. In contrast, the novel gene described herein is strongly expressed in skeletal muscle and heart tissue, with low levels of expression in the pancreas. This novel gene, RPL3L (Ribosomal Protein L3-Like), is located in a gene-rich region near the PKD1 and TSC2 genes on chromosome 16p13.3.

The RPL3L protein is more closely related to the above mentioned cytoplasmic ribosomal proteins than to previously described nucleus-encoded mitochondrial proteins (Graack *et al.*, *Eur. J. Biochem.* 206:373-380, 1992). The presence of a highly conserved nuclear localization sequence in the RPL3L further supports the hypothesis that it represents a novel cytoplasmic L3 ribosomal protein subtype and not a nucleus-encoded mitochondrial protein.

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In addition, an exon trap (Genbank Accession No. L48792) from a gene which is located telomeric of the L3-like gene was obtained (transcript M in Figure 1). Sequences encoded by transcript M were shown to have homology to pilB from *Neisseria gonorrhoeae* (Taha *et al.*, *EMBO J.* 7:4367-4378, 1988) as well as to a computer predicted 17.2 kDa protein encoded by cosmid F44E2.6 from *C. elegans* (Wilson *et al.*, *supra.*).

Using sequences from exon trap L48792, a 600 bp partial cDNA was isolated and it was determined that the corresponding gene is oriented centromeric to telomeric. A 1.3 kb message was detected by the cDNA on Northern blots. Sequences conserved between the partial cDNA and the hypothetical 17.2 kDa protein were also conserved in the pilB protein from *Neisseria gonorrhoeae* (Taha *et al.*, *supra.* 1988), a hypothetical 19.3 kDa protein from yeast (Genbank Accession No. P25566), and a fimbrial transcription regulation repressor from *Haemophilus* (Fleischmann *et al.*, *Science* 269:496-512 1995) (Figure 2). The pilB protein has homology to histidine kinase sensors and has been shown to play a role in the repression of pilin production in *Neisseria gonorrhoeae* (Taha *et al.*, *supra.* 1988; Taha *et al.*, *Mol. Microbiol.* 5:137-148, 1991). However, residues conserved between pilB, transcript M and the *C. elegans*, yeast, and *Haemophilus* sequences do not include the conserved histidine kinase domains from pilB (Taha *et al.*, *supra.* 1991). These findings suggest that the conserved region in transcript M has a function which is independent of the proposed histidine kinase sensor activity of pilB.

An additional exon trap from region of overlap between the 109.8C and 47.2H P1 clones was shown to contain human LLRep3 sequences (Slynn *et al.*, *Nuc. Acids Res.* 18:681, 1990). Hybridization studies indicated that the LLRep3 sequences (transcript K in Figure 1) were located between the *sazD* and L3-like genes. The region of highest gene density appears to be at the telomeric end of this

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cloned interval, particularly the region between TSC2 and D16S84, with a minimum of five genes mapping to this region (transcription units K, L and M, *sazD* and hERV1).

Also mapped to this region, was an exon trap which is 86% identical (170/197) at the nucleotide level to the previously described rat augmenter of liver regeneration (Hagiya *et al., Proc. Natl. Acad. Sci., USA* 91:8142-8146, 1994). ALR is a growth factor which augments the growth of damaged liver tissue while having no effect on the resting liver. Studies have demonstrated that rat ALR is capable of augmenting hepatocytic regeneration following hepatectomy.

This ALR-like exon trap was also shown to contain sequences from the recently described hERV1 gene, which encodes a functional homologue to yeast ERV1 (Lisowsky *et al., supra.*).

A 468 bp cDNA, hALR, has been obtained from the human ALR gene (Figure 13). The ALR sequences encode a 119 amino acid protein which is 84.8% identical and 94.1% similar to the rat ALR protein (Figure 14).

The cloning of human ALR has significant implications in the treatment of degenerative liver diseases. For example, biologically active rat ALR has been produced from COS-7 cells expressing rat ALR cDNA (Hagiya *et al., supra.*). Accordingly, recombinant hALR could be used in the treatment of damaged liver. In addition, a construct expressing hALR could be used in gene therapy to treat chronic liver diseases.

Forty three of the trapped exons did not have significant homology to sequences in the protein or DNA databases, nor were ESTs (expressed sequence tags) containing sequences from the exon traps observed in dbEST. The absence of ESTs containing sequences from these novel exon traps is not surprising since one of the criterion for

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selecting exon traps for further analysis was the presence of an EST in the database. These trapped exons are likely to represent *bona fide* products, since in many cases they were trapped multiple times from different P1 clones and in combination with flanking exons.

The present invention encompasses novel human genes an isolated nucleic acids comprising unique exon sequences from chromosome 16. The sequences described herein provide a valuable resource for transcriptional mapping and create a set of sequence-ready templates for a gene-rich interval responsible for at least two inheritable diseases.

Accordingly, the present invention provides isolated nucleic acids encoding human netrin (hNET), human ATP Binding Cassette transporter (hABC3), human ribosomal L3 (RPL3L) and human augmenter of liver regeneration (hALR) polypeptides. The present invention further provides isolated nucleic acids comprising unique exon sequences from chromosome 16. The term "nucleic acids" (also referred to as polynucleotides) encompasses RNA as well as single and double-stranded DNA, cDNA and oligonucleotides. As used herein, the phrase "isolated" means a polynucleotide that is in a form that does not occur in nature.

One means of isolating polynucleotides encoding invention polypeptides is to probe a human tissue-specific library with a natural or artificially designed DNA probe using methods well known in the art. DNA probes derived from the human netrin gene, hNET, the human ABC transporter gene, hABC3, the human ribosomal protein L3 gene, RPL3L, or the human augmenter of liver regeneration gene, hALR, are particularly useful for this purpose. DNA and cDNA molecules that encode invention polypeptides can be used to obtain complementary genomic DNA, cDNA or RNA from human, mammalian, or other animal sources, or to isolate related

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cDNA or genomic clones by the screening of cDNA or genomic libraries, by methods described in more detail below.

The present invention encompasses isolated nucleic acid sequences, including sense and antisense oligonucleotide sequences, derived from the sequences shown in Figures 3, 4, 8, 11 and 15. hNET-, hABC3-, RPL3L- (SEM L3-), and hALR-derived sequences may also be associated with heterologous sequences, including promoters, enhancers, response elements, signal sequences, polyadenylation sequences, and the like. Furthermore, the nucleic acids can be modified to alter stability, solubility, binding affinity, and specificity. For example, invention-derived sequences can further include nuclease-resistant phosphorothioate, phosphoroamidate, and methylphosphonate derivatives, as well as "protein nucleic acid" (PNA) formed by conjugating bases to an amino acid backbone as described in Nielsen *et al.*, *Science*, 254:1497, 1991. The nucleic acid may be derivatized by linkage of the α-anomer nucleotide, or by formation of a methyl or ethyl phosphotriester or an alkyl phosphoramidate linkage. Furthermore, the nucleic acid sequences of the present invention may also be modified with a label capable of providing a detectable signal, either directly or indirectly. Exemplary labels include radioisotopes, fluorescent molecules, biotin, and the like.

In general, nucleic acid manipulations according to the present invention use methods that are well known in the art, as disclosed in, for example, Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual 2d Ed.* (Cold Spring Harbor, NY, 1989), or Ausubel *et al.*, *Current Protocols in Molecular Biology* (Greene Assoc., Wiley Interscience, NY, NY, 1992).

Examples of nucleic acids are RNA, cDNA, or genomic DNA encoding a human netrin, a human ABC transporter, a human ribosomal L3 subtype, or a human

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augmenter of liver regeneration polypeptide. Such nucleic acids may have coding sequences substantially the same as the coding sequence shown in Figures 3, 4, 8, 11 and 15, respectively.

The present invention further provides isolated oligonucleotides corresponding to sequences within the hNET, hABC3, RPL3L (formerly SEM L3), hALR genes, or within the respective cDNAs, which, alone or together, can be used to discriminate between the authentic expressed gene and homologues or other repeated sequences. These oligonucleotides may be from about 12 to about 60 nucleotides in length, preferably about 18 nucleotides, may be single- or double-stranded, and may be labeled or modified as described below.

This invention also encompasses nucleic acids which differ from the nucleic acids shown in Figures 3, 4, 8, 11 and 15, but which have the same phenotype, i.e., encode substantially the same amino acid sequence set forth in Figures 3, 4, 8, 11 and 15, respectively. Phenotypically similar nucleic acids are also referred to as "functionally equivalent nucleic acids". As used herein, the phrase "functionally equivalent nucleic acids" encompasses nucleic acids characterized by slight and non-consequential sequence variations that will function in substantially the same manner to produce the same protein product(s) as the nucleic acids disclosed herein. In particular, functionally equivalent nucleic acids encode proteins that are the same as those disclosed herein or that have conservative amino acid variations. For example, conservative variations include substitution of a non-polar residue with another non-polar residue, or substitution of a charged residue with a similarly charged residue. These variations include those recognized by skilled artisans as those that do not substantially alter the tertiary structure of the protein.

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Further provided are nucleic acids encoding human netrin, human ABC3 transporter, human ribosomal L3 subtype, and human augmenter of liver regeneration polypeptides that, by virtue of the degeneracy of the genetic code, do not necessarily hybridize to the invention nucleic acids under specified hybridization conditions. Preferred nucleic acids encoding the invention polypeptide are comprised of nucleotides that encode substantially the same amino acid sequence set forth in Figures 4, 8, 11 and 15. Alternatively, preferred nucleic acids encoding the invention polypeptide(s) hybridize under high stringency conditions to substantially the entire sequence, or substantial portions (i.e., typically at least 12 to 60 nucleotides) of the nucleic acid sequence set forth in Figures 3, 4, 8, 11 and 15, respectively.

Stringency of hybridization, as used herein, refers to conditions under which polynucleotide hybrids are stable. As known to those of skill in the art, the stability of hybrids is a function of sodium ion concentration and temperature. (See, for example, Sambrook *et al.*, *supra*.).

The present invention provides isolated polynucleotides operatively linked to a promoter of RNA transcription, as well as other regulatory sequences. As used herein, the phrase "operatively linked" refers to the functional relationship of the polynucleotide with regulatory and effector sequences of nucleotides, such as promoters, enhancers, transcriptional and translational stop sites, and other signal sequences. For example, operative linkage of a polynucleotide to a promoter refers to the physical and functional relationship between the polynucleotide and the promoter such that transcription of DNA is initiated from the promoter by an RNA polymerase that specifically recognizes and binds to the promoter, and wherein the promoter directs the transcription of RNA from the polynucleotide.

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Promoter regions include specific sequences that are sufficient for RNA polymerase recognition, binding and transcription initiation. Additionally, promoter regions include sequences that modulate the recognition, binding and transcription initiation activity of RNA polymerase. Such sequences may be *cis* acting or may be responsive to *trans* acting factors. Depending upon the nature of the regulation, promoters may be constitutive or regulated. Examples of promoters are SP6, T4, T7, SV40 early promoter, cytomegalovirus (CMV) promoter, mouse mammary tumor virus (MMTV) steroid-inducible promoter, Moloney murine leukemia virus (MMLV) promoter, and the like.

Vectors that contain both a promoter and a cloning site into which a polynucleotide can be operatively linked are well known in the art. Such vectors are capable of transcribing RNA *in vitro* or *in vivo*, and are commercially available from sources such as Stratagene (La Jolla, CA) and Promega Biotech (Madison, WI). In order to optimize expression and/or *in vitro* transcription, it may be necessary to remove, add or alter 5' and/or 3' untranslated portions of the clones to eliminate extra, potential inappropriate alternative translation initiation codons or other sequences that may interfere with or reduce expression, either at the level of transcription or translation. Alternatively, consensus ribosome binding sites can be inserted immediately 5' of the start codon to enhance expression. Similarly, alternative codons, encoding the same amino acid, can be substituted for coding sequences of the human netrin, human ABC3 transporter, the human ribosomal L3 subtype, or the human augmenter of liver regeneration polypeptide in order to enhance transcription (e.g., the codon preference of the host cell can be adopted, the presence of G-C rich domains can be reduced, and the like).

Examples of vectors are viruses, such as baculoviruses and retroviruses, bacteriophages, cosmids, plasmids, fungal vectors and other recombination vehicles

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typically used in the art which have been described for expression in a variety of eukaryotic and prokaryotic hosts, and may be used for gene therapy as well as for simple protein expression.

Polynucleotides are inserted into vector genomes using methods well known in the art. For example, insert and vector DNA can be contacted, under suitable conditions, with a restriction enzyme to create complementary ends on each molecule that can pair with each other and be joined together with a ligase. Alternatively, synthetic nucleic acid linkers can be ligated to the termini of restricted polynucleotide. These synthetic linkers contain nucleic acid sequences that correspond to a particular restriction site in the vector DNA. Additionally, an oligonucleotide containing a termination codon and an appropriate restriction site can be ligated for insertion into a vector containing, for example, some or all of the following:a selectable marker gene, such as the neomycin gene for selection of stable or transient transfectants in mammalian cells; enhancer/promoter sequences from the immediate early gene of human CMV for high levels of transcription; transcription termination and RNA processing signals from SV40 for mRNA stability; SV40 polyoma origins of replication and ColE1 for proper episomal replication; versatile multiple cloning sites; and T7 and SP6 RNA promoters for *in vitro* transcription of sense and antisense RNA. Other means are well known and available in the art.

Also provided are vectors comprising a polynucleotide encoding human netrin, human ABC3 transporter, human ribosomal L3 subtype, and human augmenter of liver regeneration polypeptides, adapted for expression in a bacterial cell, a yeast cell, an amphibian cell, an insect cell, a mammalian cell and other animal cells. The vectors additionally comprise the regulatory elements necessary for expression of the polynucleotide in the bacterial, yeast, amphibian, mammalian or animal cells so located relative to the polynucleotide encoding human

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netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptides as to permit expression thereof. As used herein, "expression" refers to the process by which polynucleotides are transcribed into mRNA and translated into peptides, polypeptides, or proteins. If the polynucleotide is derived from genomic DNA, expression may include splicing of the mRNA, if an appropriate eukaryotic host is selected. Regulatory elements required for expression include promoter sequences to bind RNA polymerase and transcription initiation sequences for ribosome binding. For example, a bacterial expression vector includes a promoter such as the *lac* promoter and for transcription initiation the Shine-Dalgarno sequence and the start codon AUG (Sambrook *et al., supra.*). Similarly, a eukaryotic expression vector includes a heterologous or homologous promoter for RNA polymerase II, a downstream polyadenylation signal, the start codon AUG, and a termination codon for detachment of the ribosome. Such vectors can be obtained commercially or assembled by the sequences described in methods well known in the art, for example, the methods described above for constructing vectors in general. Expression vectors are useful to produce cells that express the invention receptor.

This invention provides a transformed host cell that recombinantly expresses the human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptides. Invention host cells have been transformed with a polynucleotide encoding a human netrin, a human ABC3 transporter, a human ribosomal L3 subtype, or a human augmenter of liver regeneration polypeptide. An example is a mammalian cell comprising a plasmid adapted for expression in a mammalian cell. The plasmid contains a polynucleotide encoding human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptide and the regulatory elements necessary for expression of the invention protein.

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Appropriate host cells include bacteria, archebacteria, fungi, especially yeast, plant cells, insect cells and animal cells, especially mammalian cells. Of particular interest are *E. coli*, *B. Subtilis*, *Saccharomyces cerevisiae*, SF9 cells, C129 cells, 293 cells, *Neurospora*, and CHO cells, COS cells, HeLa cells, and immortalized mammalian myeloid and lymphoid cell lines. Preferred replication systems include M13, ColE1, SV40, baculovirus, lambda, adenovirus, artificial chromosomes, and the like. A large number of transcription initiation and termination regulatory regions have been isolated and shown to be effective in the transcription and translation of heterologous proteins in the various hosts. Examples of these regions, methods of isolation, manner of manipulation, and the like, are known in the art. Under appropriate expression conditions, host cells can be used as a source of recombinantly produced hNET, hABC3, RPL3L (formerly SEM L3) and/or hALR.

Nucleic acids (polynucleotides) encoding invention polypeptides may also be incorporated into the genome of recipient cells by recombination events. For example, such a sequence can be microinjected into a cell, and thereby effect homologous recombination at the site of an endogenous gene encoding hNET, hABC3, RPL3L (formerly SEM L3), and/or hALR an analog or pseudogene thereof, or a sequence with substantial identity to a hNET-, hABC3-, RPL3L (SEM L3-), or hALR- encoding gene. Other recombination-based methods such as nonhomologous recombinations or deletion of endogenous gene by homologous recombination, especially in pluripotent cells, may also be used.

The present invention provides isolated peptides, polypeptides(s) and/or protein(s) encoded by the invention nucleic acids. The present invention also encompasses isolated polypeptides having a sequence encoded by hNET, hABC3, RPL3L (SEM L3), and hALR genes, as well as peptides

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of six or more amino acids derived therefrom. The polypeptide(s) may be isolated from human tissues obtained by biopsy or autopsy, or may be produced in a heterologous cell by recombinant DNA methods as described herein.

As used herein, the term "isolated" means a protein molecule free of cellular components and/or contaminants normally associated with a native *in vivo* environment. Invention polypeptides and/or proteins include any natural occurring allelic variant, as well as recombinant forms thereof. Invention polypeptides can be isolated using various methods well known to a person of skill in the art.

The methods available for the isolation and purification of invention proteins include, precipitation, gel filtration, and chromatographic methods including molecular sieve, ion-exchange, and affinity chromatography using e.g. hNET-, hABC3-, RPL3L- (SEM L3-), and/or hALR-specific antibodies or ligands. Other well-known methods are described in Deutscher *et al., Guide to Protein Purification: Methods in Enzymology Vol. 182,* (Academic Press, 1990). When the invention polypeptide to be purified is produced in a recombinant system, the recombinant expression vector may comprise additional sequences that encode additional amino-terminal or carboxy-terminal amino acids; these extra amino acids act as "tags" for immunoaffinity purification using immobilized antibodies or for affinity purification using immobilized ligands.

Peptides comprising hNET-, hABC3-, RPL3L- (SEM L3-) or hALR-specific sequences may be derived from isolated larger hNET, hABC3, RPL3L (SEM L3), or hALR polypeptides described above, using proteolytic cleavages by e.g. proteases such as trypsin and chemical treatments such as cyanogen bromide that are well-known in the art. Alternatively, peptides up to 60 residues in length can be

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routinely synthesized in milligram quantities using commercially available peptide synthesizers.

An example of the means for preparing the invention polypeptide(s) is to express polynucleotides encoding hNET, hABC3, RPL3L (SEM L3), and/or hALR in a suitable host cell, such as a bacterial cell, a yeast cell, an amphibian cell (i.e., oocyte), an insect cell (i.e., drosophila) or a mammalian cell, using methods well known in the art, and recovering the expressed polypeptide, again using well-known methods. Invention polypeptides can be isolated directly from cells that have been transformed with expression vectors, described below in more detail. The invention polypeptide, biologically active fragments, and functional equivalents thereof can also be produced by chemical synthesis. As used herein, "biologically active fragment" refers to any portion of the polypeptide represented by the amino acid sequence in Figures 4, 8, 11 and 15 that can assemble into an active protein. Synthetic polypeptides can be produced using Applied Biosystems, Inc. Model 430A or 431A automatic peptide synthesizer (Foster City, CA) employing the chemistry provided by the manufacturer.

Modification of the invention nucleic acids, polynucleotides, polypeptides, peptides or proteins with the following phrases: "recombinantly expressed/produced", "isolated", or "substantially pure", encompasses nucleic acids, polynucleotides, polypeptides, peptides or proteins that have been produced in such form by the hand of man, and are thus separated from their native *in vivo* cellular environment. As a result of this human intervention, the recombinant nucleic acids, polynucleotides, polypeptides, peptides and proteins of the invention are useful in ways that the corresponding naturally occurring molecules are not, such as identification of selective drugs or compounds.

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Sequences having "substantial sequence homology" are intended to refer to nucleotide sequences that share at least about 90% identity with invention nucleic acids; and amino acid sequences that typically share at least about 95% amino acid identity with invention polypeptides. It is recognized, however, that polypeptides or nucleic acids containing less than the above-described levels of homology arising as splice variants or that are modified by conservative amino acid substitutions, or by substitution of degenerate codons are also encompassed within the scope of the present invention.

The present invention provides a nucleic acid probe comprising a polynucleotide capable of specifically hybridizing with a sequence included within the nucleic acid sequence encoding human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptide, for example, a coding sequence included within the nucleotide sequence shown in Figures 3, 4, 8, 11 and 15, respectively.

As used herein, a "nucleic acid probe" may be a sequence of nucleotides that includes from about 12 to about 60 contiguous bases set forth in Figures 3, 4, 8, 11 and 15, preferably about 18 nucleotides, may be single- or double-stranded, and may be labeled or modified as described herein. Preferred regions from which to construct probes include 5' and/or 3' coding sequences, sequences predicted to encode transmembrane domains, sequences predicted to encode cytoplasmic loops, signal sequences, ligand binding sites, and the like.

Full-length or fragments of cDNA clones can also be used as probes for the detection and isolation of related genes. When fragments are used as probes, preferably the cDNA sequences will be from the carboxyl end-encoding portion of the cDNA, and most preferably will include predicted transmembrane domain-encoding portions of the cDNA sequence. Transmembrane domain regions can be

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predicted based on hydropathy analysis of the deduced amino acid sequence using, for example, the method of Kyte and Doolittle (*J. Mol. Biol.* 157:105, 1982).

As used herein, the phrase "specifically hybridizing" encompasses the ability of a polynucleotide to recognize a sequence of nucleic acids that are complementary thereto and to form double-helical segments via hydrogen bonding between complementary base pairs. Nucleic acid probe technology is well known to those skilled in the art who will readily appreciate that such probes may vary greatly in length and may be labeled with a detectable agent, such as a radioisotope, a fluorescent dye, and the like, to facilitate detection of the probe. Invention probes are useful to detect the presence of nucleic acids encoding human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptides. For example, the probes can be used for *in situ* hybridizations in order to locate biological tissues in which the invention gene is expressed. Additionally, synthesized oligonucleotides complementary to the nucleic acids of a polynucleotide encoding human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptides are useful as probes for detecting the invention genes, their associated mRNA, or for the isolation of related genes using homology screening of genomic or cDNA libraries, or by using amplification techniques well known to one of skill in the art.

Also provided are antisense oligonucleotides having a sequence capable of binding specifically with any portion of an mRNA that encodes human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptide so as to prevent translation of the mRNA. The antisense oligonucleotide may have a sequence capable of binding specifically with any portion of the sequence of the cDNA encoding human netrin, human ABC3 transporter, human ribosomal L3 subtype, or

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human augmenter of liver regeneration polypeptide. As used herein, the phrase "binding specifically" encompasses the ability of a nucleic acid sequence to recognize a complementary nucleic acid sequence and to form double-helical segments therewith via the formation of hydrogen bonds between the complementary base pairs. An example of an antisense oligonucleotide is an antisense oligonucleotide comprising chemical analogs of nucleotides (i.e., synthetic antisense oligonucleotide, SAO).

Compositions comprising an amount of the antisense oligonucleotide, (SAOC), effective to reduce expression of the human netrin, the human ABC3 transporter, the human ribosomal L3 subtype, or the human augmenter of liver regeneration polypeptide by passing through a cell membrane and binding specifically with mRNA encoding the human netrin, the human ABC3 transporter, the human ribosomal L3 subtype, or the human augmenter of liver regeneration polypeptide so as to prevent its translation and an acceptable hydrophobic carrier capable of passing through a cell membrane are also provided herein. The acceptable hydrophobic carrier capable of passing through cell membranes may also comprise a structure which binds to a receptor specific for a selected cell type and is thereby taken up by cells of the selected cell type. The structure may be part of a protein known to bind to a cell-type specific receptor.

This invention provides a means to modulate levels of expression of invention polypeptides by the use of a synthetic antisense oligonucleotide composition (SAOC) which inhibits translation of mRNA encoding these polypeptides. Synthetic oligonucleotides, or other antisense chemical structures designed to recognize and selectively bind to mRNA, are constructed to be complementary to portions of the nucleotide sequences shown in Figures 3, 4, 8, 11 and 15, of DNA, RNA or chemically modified, artificial nucleic acids. The SAOC is designed to be stable in the blood stream for administration to a

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subject by injection, or in laboratory cell culture conditions. The SAOC is designed to be capable of passing through the cell membrane in order to enter the cytoplasm of the cell by virtue of physical and chemical properties of the SAOC which render it capable of passing through cell membranes, for example, by designing small, hydrophobic SAOC chemical structures, or by virtue of specific transport systems in the cell which recognize and transport the SAOC into the cell.

In addition, the SAOC can be designed for administration only to certain selected cell populations by targeting the SAOC to be recognized by specific cellular uptake mechanisms which bind and take up the SAOC only within select cell populations. For example, the SAOC may be designed to bind to a receptor found only in a certain cell type, as discussed *supra*. The SAOC is also designed to recognize and selectively bind to the target mRNA sequence, which may correspond to a sequence contained within the sequence shown in Figures 3, 4, 8, 11 and 15. The SAOC is designed to inactivate the target mRNA sequence by either binding to the target mRNA and inducing degradation of the mRNA by, for example, RNase I digestion, or inhibiting translation of the mRNA target by interfering with the binding of translation-regulating factors or ribosomes, or inclusion of other chemical structures, such as ribozyme sequences or reactive chemical groups which either degrade or chemically modify the target mRNA. SAOCs have been shown to be capable of such properties when directed against mRNA targets (see Cohen *et al.*, *TIPS*, 10:435, 1989 and Weintraub, *Sci. American*, January pp.40, 1990).

This invention further provides a composition containing an acceptable carrier and any of an isolated, purified human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptide, an active fragment thereof, or a purified, mature protein and active fragments thereof,

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alone or in combination with each other. These polypeptides or proteins can be recombinantly derived, chemically synthesized or purified from native sources. As used herein, the term "acceptable carrier" encompasses any of the standard pharmaceutical carriers, such as phosphate buffered saline solution, water and emulsions such as an oil/water or water/oil emulsion, and various types of wetting agents.

Also provided are antibodies having specific reactivity with the human netrin, the human ABC3 transporter, the human ribosomal L3 subtype, or the human augmenter of liver regeneration polypeptides of the subject invention. Active fragments of antibodies are encompassed within the definition of "antibody". Invention antibodies can be produced by methods known in the art using the invention proteins or portions thereof as antigens. For example, polyclonal and monoclonal antibodies can be produced by methods well known in the art, as described, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual* (Cold Spring Harbor Laboratory 1988).

The polypeptides of the present invention can be used as the immunogen in generating such antibodies. Alternatively, synthetic peptides can be prepared (using commercially available synthesizers) and used as immunogens. Where natural or synthetic hNET-, hABC3-, RPL3L- (SEM L3-), and/or hALR-derived peptides are used to induce a hNET-, hABC3-, RPL3L- (SEM L3-), and/or hALR-specific immune response, the peptides may be conveniently coupled to an suitable carrier such as KLH and administered in a suitable adjuvant such as Freund's. Preferably, selected peptides are coupled to a lysine core carrier substantially according to the methods of Tam, *Proc. Natl. Acad. Sci, USA* 85:5409-5413, 1988. The resulting antibodies may be modified to a monovalent form, such as, for example, Fab, Fab_2, FAB', or FV. Anti-idiotypic antibodies may also be prepared using known methods.

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In one embodiment, normal or mutated hNET, hABC3, RPL3L (SEM L3), or hALR polypeptides are used to immunize mice, after which their spleens are removed, and splenocytes used to form cell hybrids with myeloma cells and obtain clones of antibody-secreted cells according to techniques that are standard in the art. The resulting monoclonal antibodies are screened for specific binding to hNET, hABC3, RPL3L (SEM L3), and/or hALR proteins or hNET-, hABC3-, RPL3L- (SEM L3-), and/or hALR-related peptides.

In another embodiment, antibodies are screened for selective binding to normal or mutated hNET, hABC3, RPL3L (SEM L3), or hALR sequences. Antibodies that distinguish between normal and mutant forms of hNET, hABC3, RPL3L (SEM L3), or hALR may be used in diagnostic tests (see below) employing ELISA, EMIT, CEDIA, SLIFA, and the like. Anti- hNET, hABC3, RPL3L (SEM L3), or hALR antibodies may also be used to perform subcellular and histochemical localization studies. Finally, antibodies may be used to block the function of the hNET, hABC3, RPL3L (SEM L3), and/or hALR polypeptide, whether normal or mutant, or to perform rational drug design studies to identify and test inhibitors of the function (e.g., using an anti-idiotypic antibody approach).

Amino acid sequences can be analyzed by methods well known in the art to determine whether they encode hydrophobic or hydrophilic domains of the corresponding polypeptide. Altered antibodies such as chimeric, humanized, CDR-grafted or bifunctional antibodies can also be produced by methods well known in the art. Such antibodies can also be produced by hybridoma, chemical synthesis or recombinant methods described, for example, in Sambrook *et al.*, *supra.*, and Harlow and Lane, *supra*. Both anti-peptide and anti-fusion protein antibodies can be used. (see, for example, Bahouth *et al.*, *Trends Pharmacol. Sci.* 12:338, 1991; Ausubel *et al.*, *supra.*).

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Invention antibodies can be used to isolate invention polypeptides. Additionally, the antibodies are useful for detecting the presence of the invention polypeptides, as well as analysis of polypeptide localization, composition, and structure of functional domains. Methods for detecting the presence of a human netrin, a human ABC3 transporter, a human ribosomal L3 subtype, or a human augmenter of liver regeneration polypeptide comprise contacting the cell with an antibody that specifically binds to the polypeptide, under conditions permitting binding of the antibody to the polypeptide, detecting the presence of the antibody bound to the cell, and thereby detecting the presence of the invention polypeptide on the cell. With respect to the detection of such polypeptides, the antibodies can be used for *in vitro* diagnostic or *in vivo* imaging methods.

Immunological procedures useful for *in vitro* detection of the target human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptide in a sample include immunoassays that employ a detectable antibody. Such immunoassays include, for example, ELISA, Pandex microfluorimetric assay, agglutination assays, flow cytometry, serum diagnostic assays and immunohistochemical staining procedures which are well known in the art. An antibody can be made detectable by various means well known in the art. For example, a detectable marker can be directly or indirectly attached to the antibody. Useful markers include, for example, radionuclides, enzymes, fluorogens, chromogens and chemiluminescent labels.

For *in vivo* imaging methods, a detectable antibody can be administered to a subject and the binding of the antibody to the invention polypeptide can be detected by imaging techniques well known in the art. Suitable imaging agents are known and include, for example, gamma-emitting radionuclides such as ^{111}In, ^{99m}Tc, ^{51}Cr and the like, as well as paramagnetic metal ions, which are

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described in U.S. Patent No. 4,647,447. The radionuclides permit the imaging of tissues by gamma scintillation photometry, positron emission tomography, single photon emission computed tomography and gamma camera whole body imaging, while paramagnetic metal ions permit visualization by magnetic resonance imaging.

The invention provides a transgenic non-human mammal that is capable of expressing nucleic acids encoding a human netrin, a human ABC3 transporter, a human ribosomal L3 subtype, or a human augmenter of liver regeneration polypeptide. Also provided is a transgenic non-human mammal capable of expressing nucleic acids encoding a human netrin, a human ABC3 transporter, a human ribosomal L3 subtype, or a human augmenter of liver regeneration polypeptide so mutated as to be incapable of normal activity, i.e., does not express native protein.

The present invention also provides a transgenic non-human mammal having a genome comprising antisense nucleic acids complementary to nucleic acids encoding human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptide so placed as to be transcribed into antisense mRNA complementary to mRNA encoding a human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptide, which hybridizes thereto and, thereby, reduces the translation thereof. The polynucleotide may additionally comprise an inducible promoter and/or tissue specific regulatory elements, so that expression can be induced, or restricted to specific cell types. Examples of polynucleotides are DNA or cDNA having a coding sequence substantially the same as the coding sequence shown in Figures 3, 4, 8, 11 and 15. Examples of non-human transgenic mammals are transgenic cows, sheep, goats, pigs, rabbits, rats and mice. Examples of tissue specificity-determining elements are the metallothionein promoter and the T7 promoter.

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Animal model systems which elucidate the physiological and behavioral roles of invention polypeptides are produced by creating transgenic animals in which the expression of the polypeptide is altered using a variety of techniques. Examples of such techniques include the insertion of normal or mutant versions of nucleic acids encoding human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptide by microinjection, retroviral infection or other means well known to those skilled in the art, into appropriate fertilized embryos to produce a transgenic animal. See, for example, Carver *et al.*, *Bio/Technology* 11:1263-1270, 1993; Carver *et al.*, *Cytotechnology* 9:77-84, 1992; Clark *et al.*, *Bio/Technology* 7:487-492, 1989; Simons *et al.*, *Bio/Technology* 6:179-183, 1988; Swanson *et al.*, *Bio/Technology* 10:557-559, 1992; Velander *et al.*, *Proc. Natl. Acad. Sci., USA* 89:12003-12007, 1992; Hammer *et al.*, *Nature* 315:680-683, 1985; Krimpenfort *et al.*, *Bio/Technology* 9:844-847, 1991; Ebert *et al.*, *Bio/Technology* 9:835-838, 1991; Simons *et al.*, *Nature* 328:530-532, 1987; Pittius *et al.*, *Proc. Natl. Acad. Sci., USA* 85:5874-5878, 1988; Greenberg *et al.*, *Proc. Natl. Acad. Sci., USA* 88:8327-8331, 1991; Whitelaw *et al.*, *Transg. Res.* 1:3-13, 1991; Gordon *et al.*, *Bio/Technology* 5:1183-1187, 1987; Grosveld *et al.*, *Cell* 51:975-985, 1987; Brinster *et al.*, *Proc. Natl. Acad. Sci., USA* 88:478-482, 1991; Brinster *et al.*, *Proc. Natl. Acad. Sci., USA* 85:836-840, 1988; Brinster *et al.*, *Proc. Natl. Acad. Sci., USA* 82:4438-4442, 1985; Al-Shawi *et al.*, *Mol. Cell. Biol.* 10(3):1192-1198, 1990; Van Der Putten *et al.*, *Proc. Natl. Acad. Sci., USA* 82:6148-6152, 1985; Thompson *et al.*, *Cell* 56:313-321, 1989; Gordon *et al.*, *Science* 214:1244-1246, 1981; and Hogan *et al.*, *Manipulating the Mouse Embryo: A Laboratory Manual* (Cold Spring Harbor Laboratory, 1986).

Another technique, homologous recombination of mutant or normal versions of these genes with the native gene locus in transgenic animals, may be used to alter the regulation of expression or the structure of the invention

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polypeptides (see, Capecchi *et al.*, *Science* 244:1288, 1989; Zimmer *et al.*, *Nature* 338:150, 1989). Homologous recombination techniques are well known in the art. Homologous recombination replaces the native (endogenous) gene with a recombinant or mutated gene to produce an animal that cannot express native (endogenous) protein but can express, for example, a mutated protein which results in altered expression of the human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptide.

In contrast to homologous recombination, microinjection adds genes to the host genome, without removing host genes. Microinjection can produce a transgenic animal that is capable of expressing both endogenous and exogenous human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptides. Inducible promoters can be linked to the coding region of the nucleic acids to provide a means to regulate expression of the transgene. Tissue-specific regulatory elements can be linked to the coding region to permit tissue-specific expression of the transgene. Transgenic animal model systems are useful for *in vivo* screening of compounds for identification of ligands, i.e., agonists and antagonists, which activate or inhibit polypeptide responses.

The nucleic acids, oligonucleotides (including antisense), vectors containing same, transformed host cells, polypeptides, as well as antibodies of the present invention, can be used to screen compounds *in vitro* to determine whether a compound functions as a potential agonist or antagonist to the invention protein. These *in vitro* screening assays provide information regarding the function and activity of the invention protein, which can lead to the identification and design of compounds that are capable of specific interaction with invention proteins.

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In accordance with still another embodiment of the present invention, there is provided a method for identifying compounds which bind to human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptides. The invention proteins may be employed in a competitive binding assay. Such an assay can accommodate the rapid screening of a large number of compounds to determine which compounds, if any, are capable of binding to invention polypeptides. Subsequently, more detailed assays can be carried out with those compounds found to bind, to further determine whether such compounds act as modulators, agonists or antagonists of invention polypeptides.

In accordance with another embodiment of the present invention, transformed host cells that recombinantly express invention polypeptides can be contacted with a test compound, and the modulating effect(s) thereof can then be evaluated by comparing the human netrin, human ABC3 transporter, human ribosomal L3 subtype, or human augmenter of liver regeneration polypeptide-mediated response in the presence and absence of test compound, or by comparing the response of test cells or control cells (i.e., cells that do not express invention polypeptides), to the presence of the compound.

As used herein, a compound or a signal that "modulates the activity" of an invention polypeptide refers to a compound or a signal that alters the activity of the human netrin, the human ABC3 transporter, the human ribosomal L3 subtype, or the human augmenter of liver regeneration polypeptide so that the activity of the invention polypeptide is different in the presence of the compound or signal than in the absence of the compound or signal. In particular, such compounds or signals include agonists and antagonists. An agonist encompasses a compound or a signal that activates polypeptide function. Alternatively, an antagonist includes a compound or signal that interferes with polypeptide function. Typically, the

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effect of an antagonist is observed as a blocking of agonist-induced protein activation. Antagonists include competitive and non-competitive antagonists. A competitive antagonist (or competitive blocker) interacts with or near the site specific for agonist binding. A non-competitive antagonist or blocker inactivates the function of the polypeptide by interacting with a site other than the agonist interaction site.

The following examples are intended to illustrate the invention without limiting the scope thereof.

Example I: Contig Assembly

A. Cosmids

Multiple cosmids were used as reagents to initiate walks in YAC and P1 libraries. Clones 16-166N (D16S277), 16-191N (D16S279), 16-198N (D16S280) and 16-140N (D16S276) were previously isolated from a cosmid library (Lerner *et al.*, *Mamm. Genome* 3:92-100, 1992). Cosmids cCMM65 (D16S84), c291 (D16S291), cAJ42 (ATP6C) and cKG8 were recovered from total human cosmid libraries (made in-house or by Stratagene, La Jolla, CA) using either a cloned insert (CMM65) or sequence-specific oligonucleotides as probe. The c326 cosmid contig and clone 413C12 originated from a flow-sorted chromosome 16 library (Stallings *et al.*, *Genomics* 13(4):1031-1039, 1992). The c326 contig was comprised of clones 2H2, 77E8, 325A11 and 325B10.

B. YACs

Screening of gridded interspersed-repetitive sequence (IRS pools from Mark I, Mark II and Mega-YAC libraries) with cosmid-specific IRS probes was as previously described (Liu *et al.*, *Genomics* 26:178-191, 1995). IRS probes were made from cosmids 16-166N, 16-191N, cAJ42, 16-198N, 325A11, cCMM65, and 16-140N. Biotinylated YAC probes were generated by nick-translating complex mixtures of IRS products from each YAC. Mixtures of

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sufficient complexity were achieved by performing independent DNA amplifications of total yeast DNA using various Alu primers (Lichter *et al., Proc. Natl. Acad. Sci., USA* 87:6634-6638, 1990) and then combining the appropriate reactions containing the most diverse products.

C. P1s

Chromosome walking experiments were done using a single set of membranes which contained the gridded P1 library pools (Shepherd *et al., supra.* 1994). The gridded filters were kindly provided by Dr. Mark Leppert and the Technology Access Section of the Utah Center for Human Genome Research at the University of Utah. P1 gridded membranes were screened using end probes derived from a set of chromosome 16 cosmids (see above) and P1 clones as they were identified. Both RNA transcripts and bubble-PCR products were utilized as end probes.

D. Probes

Radiolabeled transcripts were generated using restriction enzyme digested cosmids or P1s (*AluI, HaeIII, RsaI, TaqI*) as template for phage RNA polymerases T3, T7 and SP6. The T3 and T7 promoter elements were present on the cosmid-derived templates while T7 and SP6 promoter sequences were contained on the P1-based templates. Transcription reactions were performed as recommended by the manufacturer (Stratagene, La Jolla, CA) in the presence of $[\alpha P^{32}]$-ATP (Amersham, Arlington Heights, IL).

Bubble-PCR products were synthesized from restriction enzyme digested P1s (*AluI, HaeIII, RsaI, TaqI*). Bubble adaptors with appropriate overhangs and phosphorylated 5' ends were ligated to digested P1 DNA basically as described for YACs (Riley *et al., Nuc. Acids Res.* 18:2887-2890, 1990). The sequence of the universal vectorette primer derived from the bubble adaptor sequence was 5'-GTTCGTACGAGAATCGCT-3' (SEQ ID NO:67), and differed from that of Riley and co-workers with 12 fewer 5'

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nucleotides. The T_m of the truncated vectorette primer more closely matched that of the paired amplimer from the vector-derived promoter sequence (SP6, T7). The desired bubble-PCR product was gel purified prior to radiolabeling (Feinberg *et al.*, *Anal. Biochem.* 132:6-13, 1983; Feinberg and Vogelstein, *Anal. Biochem.* 137:266-267, 1984).

The specificity of all end probes was determined prior to their use on the single set of gridded P1 filter arrays. Radiolabeled probes were pre-annealed to *Cot1* DNA as recommended (Life Technologies Inc., Gaithersburg, MD) and then hybridized to strips of nylon membrane to which were bound 10-20 ng each of the following DNAs: the cloned genomic template used to create the probe; one or more unrelated cloned genomic DNAs; cloned vector (no insert); and human genomic DNA.

Hybridizations were performed in CAK solution (5x SSPE, 1% SDS, 5x Denhardt's Solution, 100 mg/mL torula RNA) at 65°C overnight. Individual end probes were present at a concentration of $5x10^5$ cpm/mL. Hybridized membranes were washed to a final stringency of 0.1x SSC/0.1% SDS at 65° C. The hybridization results were visualized by autoradiography. Probes which hybridized robustly to their respective cloned template while not hybridizing to unrelated cloned DNAs, vector DNA or genomic DNA were identified and used to screen the gridded P1 filters.

Hybridization to the arrayed P1 pools was performed as described for the nylon membrane strips (above) except that multiple probes were used simultaneously. Positive clones were identified, plated at a density of 200-500 cfu per 100 mm plate (LB plus 25 mg/mL kanamycin), lifted onto 82 mm HATF membranes (Millipore, Bedford, MA), processed for hybridization (Sambrook *et al.*, *supra.*) and then rescreened with the complex probe mixture.

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A single positive clone from each pool was selected and replated onto a master plate. To identify the colony purified genomic P1 clone and its corresponding probe, multiple P1 DNA dot blots were prepared and each hybridized to individual radiolabeled probes. All hybridizations contained a chromosome 16p13.3 reference probe, e.g. cAJ42, as well as a uniquely labeled P1 DNA probe.

Example II: Exon Trapping

Genomic P1 clones were prepared for exon trapping experiments by digestion with *PstI*, double digestion with *BamHI/BglII*, or by partial digestion with limiting amounts of *Sau3AI*. Digested P1 DNAs were ligated to *BamHI*-cut and dephosphorylated vector, pSPL3B, while *PstI*-digested P1 DNA was subcloned into *PstI*-cut dephosphorylated vector, pSPL3B.

Ligations were performed in triplicate using 50 ng of vector DNA and 1, 3 or 6 mass equivalents of digested P1 DNA. Transformations were performed following an overnight 16°C incubation, with 1/10 and 1/2 of the transformation being plated on LB (ampicillin) plates. After overnight growth at 37°C, colonies were scraped off those plates having the highest transformation efficiency (based on a comparison to "no insert" ligation controls) and miniprepped using the alkaline lysis method. To examine the proportion of the pSPL3B containing insert, a small portion of the miniprep was digested with HindIII, which cuts pSPL3B on each side of the multiple cloning site.

Example III: RNA Preparation

Approximately 10 µg of the remaining miniprep DNA was ethanol precipitated, resuspended in 100 µl of sterile PBS and electroporated into approximately 2 x 10^6 COS-7 cells (in 0.7 ml of ice cold PBS) using a BioRad GenePulser

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electroporator (1.2 kV, 25 μF and 200 Ω). The electroporated cells were incubated for 10 min. on ice prior to their addition to a 100 mm tissue culture dish containing 10 ml of prewarmed complete DMEM.

Cytoplasmic RNA was isolated 48 hours post-transfection. The transfected COS-7 cells were removed from tissue culture dishes using 0.25% trypsin/1 mM EDTA (Life Technologies Inc., Gaithersburg, MD). Trypsinized cells were washed in DMEM/10% FCS and resuspended in 400 μl of ice cold TKM (10 mM Tris-HCl pH 7.5, 10 mM KCl, 1 mM $MgCl_2$) supplemented with 1 μl of RNAsin (Promega, Madison, WI). After adding 20 μl of 10% Triton X-100, the cells were incubated for 5 min. on ice. The nuclei were removed by centrifugation at 1200 rpm for 5 min. at 4°C. Thirty microliters of 5% SDS was added to the supernatant, with the cytoplasmic RNA being further purified by three rounds of extraction using phenol/chloroform/isoamyl alcohol (24:24:1). The cytoplasmic RNA was ethanol precipitated and resuspended in 50 μl of H_2O.

Reverse transcription and PCR were performed on the cytoplasmic RNA prepared above as described (Church *et al., supra.* 1994) using commercially available exon trapping oligonucleotides (Life Technologies Inc., Gaithersburg, MD). The resulting CUA-tailed products were shotgun subcloned into pAMP10 as recommended by the manufacturer (Life Technologies Inc.). Random clones from each ligation were analyzed by colony PCR using secondary PCR primers (Life Technologies Inc.).

Miniprep DNA containing the pAMP10/exon traps was prepared from overnight cultures by alkaline lysis using the EasyPrep manifold or a QIAwell 8 system according to the manufacturers' instructions (Pharmacia, Pistcataway, NJ and Qiagen Inc., Chatsworth, CA, respectively). DNA products containing trapped exons, based on comparison to

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the 177 bp "vector only" DNA product, were selected for sequencing.

Example IV: Sequencing

DNA sequencing was performed using Pharmacia ALF and Applied Biosystems 377 PRISM automated DNA sequencers (Piscataway, NJ, and Foster City, CA). DNA sequences were aligned using Sequencher DNA analysis software (Genecodes, Ann Arbor, MI). DNA and protein database searches were performed using the BLASTN (Altschul *et al.*, *J. Mol. Biol.* 215:403-410, 1990) and BLASTX (Altschul *et al.*, *supra.* 1990; Gish *et al.*, *Nat. Genet.* 3:266-272, 1993) programs. SASE sequences were analyzed by processing BLAST (Altschul *et al.*, *supra.* 1990; Gish *et al.*, *supra.* 1993) and FASTA (Lipman *et al.*, *Science* 227:1435-1441, 1985) searches. Protein sequences were analyzed using MacVector (Oxford Molecular Group, Cambell, CA), BCM Launcher (Smith *et al.*, *Genome Research* 6:454-462, 1996), ClustalW (Thompson *et al.*, *Nucleic Acids Res.* 22:4673-4680, 1994), and PSORT (Nakai *et al.*, *Genomics* 14:897-911 1992).

Example V: RT-PCR, RACE, SASE and cDNA Isolation

Based upon the sequence determined (above) two oligonucleotide primers (Table II) were designed for each exon trap using Oligo 4.0 (National Biosciences Inc., Plymouth, MN).

To determine which tissue-specific library to screen for transcript or cDNA, RT-PCR reactions and/or PCR reactions were performed using different tissue-derived RNAs and/or cDNA libraries, respectively, as template with the oligonucleotide primers designed for each exon trap (above).

The oligonucleotides designed from the exons (Table II), were then used in one or more of the following

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positive selection formats to screen the corresponding tissue-specific cDNA library.

For RT-PCR experiments, the first oligonucleotide was used as a sense primer and the second oligonucleotide was used as an antisense primer. RT-PCR was performed as described using polyA$^+$ RNA from adult brain and placenta (Kawasaki, In *PCR Protocols: A Guide to Methods and Applications*, Eds. Innis *et al.*, Academic Press, San Diego, CA, pp. 21-27, 1990). All PCR products were cloned using the pGEM-T vector as described by the manufacturer (Promega, Madison, WI).

To clone sequences 3' to selected exon traps, rapid amplification of cDNA ends (RACE) was performed as described (Frohman, *PCR Met. Appl.* 4:S40-S58, 1994). In 3' RACE experiments, the first oligonucleotide was used as the external primer and the second oligonucleotide was used as the internal primer.

For the Genetrapper cDNA Positive Selection System, the first oligonucleotide primer was biotinylated and used for direct selection, while the second oligonucleotide was used in the repair.

In addition to exon trapping, the cloned contig was also screened using cDNA selection essentially as described (Parimoo *et al.*, *Anal. Biochem.* 228:1-17 1995), using the genomic P1 clones from this interval (Dackowski *et al.*, *Genome Res.* 6:515-524, 1996). Other coding sequence was obtained by SAmple SEquencing (SASE).

SASE was performed as a functional genomics method for gene identification. Briefly, DNA from individual P1s were partially digested with Sau3A and 3 kb fragments were subcloned into the pBluescriptKS$^+$ plasmid (Stratagene, La Jolla, CA). Subclones were sequenced from both ends to generate sequences semi-randomly from the P1 clone.

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Example VI: Nucleotide Sequence Analysis

hNET: A random shotgun library was prepared from the 53.8B P1 clone (Figure 18) by subcloning randomly sheared P1 DNA into the pAMP10 vector (Life Technologies Inc., Gaithersburg, MD) essentially as described (Andersson *et al.*, (1994) *Anal. Biochem.* 218:300-308). P1 DNA was randomly sheared using a nebulizer (Hudson RCI, Temecula, CA). The library was initially screened with a 6 kb *Xho*I fragment, which had been shown to contain the netrin encoding exon traps (Figure 18). The library was subsequently screened with an adjacent 3.5 kb *Xho*I fragment in order to obtain additional clones for sequencing. Positive clones were sequenced using forward and reverse vector primers as previously described (The American PKD1 Consortium (1995) *Hum. Mol. Genet.* 4:575-582).

The genomic sequence was edited and assembled using Sequencher (GeneCodes, Ann Arbor, MI). The coding region was predicted using the World Wide Web version of the GRAIL2 program (Uberbacher and Mural (1991) *Proc. Natl. Acad. Sci., USA* 88:11261-11265; Xu *et al.* (1994) *Genet. Eng. N.Y.* 16:241-253) and a MacVector (Oxford Molecular Group, Cambell, CA) Pustell DNA/protein matrix analysis comparing the genomic sequence (translated in all reading frames) to the chicken netrins. Database searches were performed using BLASTN (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410) and BLASTX (Altschul *et al.*, 1990, *supra;* Gish and States (1993) *Nat. Genet.* 3:266-272).

RT-PCR: Both adult (brain, heart, kidney, leukocytes, liver, lung, a lymphoblastoid cell line, placenta, spleen, and testis) and fetal (kidney and brain) cDNA libraries were prescreened for the presence of netrin cDNAs by PCR as described (Van Raay *et al.*, 1996, *supra*). Nested RT-PCR was utilized to clone transcribed sequences from the netrin gene. Briefly, spinal cord polyA+ RNA (Clontech, Palo Alto, CA) was reverse transcribed using

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random primers as described (Kawasaki, 1990 *In* "PCR Protocols: A Guide to Methods and Applications" (M.A. Innis, D.H. Gelfand, J.J. Sninsky, and T.J. White. Eds.), pp. 21-27, Academic Press, Inc., San Diego).

Primers for PCR (Table IV) were designed based on the exons predicted from the analysis of the genomic sequence and used to amplify spinal cord RNA since spinal cord has been previously shown to express low levels of chicken netrin (Serafini *et al. supra.*). Nested PCR was required to detect RT-PCR products from human spinal cord RNA. Spinal cord RNA was reverse transcribed with random primers and primary PCR was performed in the presence of 2.5 M betaine (Sigma Chemical Co., St. Louis, MO) using the primers designed from the gene model (Table IV). The primary PCR reactions were then diluted 1:20 and secondary PCR was performed on 1 µL of the diluted primary reactions using nested primers (also designed from the gene model), again in the presence of betaine. The inclusion of betaine at a final concentration of 2.5 M in the PCR reactions dramatically increased the purity and yield of the human netrin RT-PCR products (see, for example, International Publication No. WO 96/12041; Reeves *et al.* (1994) *Am. J. Hum. Genet.* 55:A238; Baskaran *et al.* (1996) *Genome Research* 6:633-638).

RT-PCR products were subcloned using pGEM-T (Promega, Madison, WI) as recommended by the manufacturer. The resulting RT-PCR clones were sequenced with vector primers and internal primers using the ABI dye terminator chemistry (Perkin Elmer, Foster City, CA) and an ABI 377 automated sequencer (Perkin Elmer, Foster City, CA). Multiple sequence alignments were performed using ClustalW (Thompson *et al.*, (1994) *Nucleic Acids Res.* 22:4673-4680).

Sequence analysis of the RT-PCR products indicated that hNET contains at least six exons. The RT-PCR data indicate that the fourth predicted exon is actually split by an intron in the human netrin gene and is

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present as two exons. Three of the RT-PCR exons were shown to be identical to the original exon traps. Aside from the extra exon, the gene model is nearly identical to the RT-PCR products. The cDNA coding sequence, predicted protein product and full length sequence are shown in Figures 4A through 4C, respectively.

Northern blot analysis: Genomic and RT-PCR probes were radiolabeled (Feinberg and Vogelstein, *Anal. Biochem.* 132:6-13, 1983) and used to probe Northern blots containing RNAs from a variety of adult tissues (Clontech, Palo Alto, CA), including a panel of RNAs from different neural tissues including spinal cord. In addition, a human RNA Master Blot (Clontech, Palo Alto, CA) containing RNAs from 50 different adult and fetal tissues was screened as recommended by the manufacturer.

hABC3: A human lung cDNA library (LTI, Gaithersburg, MD) was screened with the GeneTrapper system (LTI, Gaithersburg, MD) using capture and repair oligonucleotides (5'-CATTGCCCGTGCTGTCGTG-3' (SEQ ID NO:52) and 5'-CATCGCCGCCTCCTTCATG-3' (SEQ ID NO:53), respectively) designed from trapped exon L48757, the 5' most trapped exon with homology to murine ABC1. Direct cDNA library screening was also performed using an RT-PCR clone as probe. 5' RACE (Frohman, M.A. in *Methods Enzymol.* (J.N. Abelson and M.I. Simon Eds.) pp. 340-356, Academic Press, San Diego, CA 1993) was used to isolate additional 5' sequences from the ABC3 transcript.

Northern blot analysis: A 679 bp fragment from the 3' untranslated region (UTR) of the ABC3 cDNA was radiolabeled by random priming (Feinberg *et al., supra.* 1983) and used to probe a multiple tissue northern blot (Clontech, Palo Alto, CA) under conditions recommended by the manufacturer.

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Identification of coding sequence for the novel ABC transporter: The gene for a novel ATP binding cassette (ABC) transporter, designated ABC3, has been mapped to the PKD1 locus on chromosome 16 (Burn *et al.*, *Genome Res.* 6:525-537, 1996). Eight exons from the hABC3 gene were obtained from the 30.1F, 64.12C and 96.4B P1 clones using exon trapping. See, Figure 16 showing the genomic interval surrounding the hABC3 gene at the top, with *NotI* sites, DNA markers, and distance in kilobases (in kb) also being shown. Genomic P1 clones from the interval which contain sequence from the hABC3 gene are shown below the genomic map. The relative position of the hABC3 cDNA is provided below the P1 clones, with the selected cDNA, trapped exons, RT-PCR clones, and cDNAs being indicated. Trapped exons and RT-PCR clones used in the isolation of additional hABC3 sequences have been labeled. The discontinuity in the line for clone ABCgt.1 represents the absence of an alternatively spliced exon.

Seven of these trapped exons encoded sequences having homology to murine ABC1 and ABC2 based on BLASTX analysis (Altschul *et al.*, *supra*. 1990; Gish *et al.*, *supra*. 1993), with sequences from the trapped exons L48758, L48759, and L48760 having highest homology. Sequences encoded by the trapped exon L48760 also had homology to a *Caenorhabditis elegans* ABC transporter predicted from genomic sequence (Wilson *et al.*, *supra*.).

cDNA selection yielded a single 261 bp cDNA clone which mapped near the 5' end of the ABC3 gene. Like L48760, this clone encoded sequences having homology to the hypothetical *C. elegans* ABC transporter. Initial analysis of the SASE results from the 30.1F P1 clone indicated that 4 of the 164 reactions encoded sequences with homology to ABC1 or ABC2. Subsequent comparison of the SASE data to the final hABC3 cDNA indicated that an additional seven sequencing reactions contained coding sequences from the ABC3 gene. A total of 1.6 kb of ABC3 coding sequence aligned with the SASE data. In that only 3.5 kb of coding

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sequence from the 5' end of the hABC3 gene map to the 30.1F P1 clone, this represents a level of 45% coverage for the SASE analysis.

Assembly and analysis of a cDNA for the novel ABC transporter: Two complementary approaches were employed to assemble the full-length hABC3 cDNA. First, RT-PCR was utilized to link the trapped exons, selected cDNA, and SASE data. Secondly, cDNA library screening was performed using direct selection as well as radiolabeled probes.

Using primers designed from the trapped exons L48757, L48758, L48760 and L75924, three RT-PCR products, containing 3.3 kb of coding sequence were cloned (Table I and Figure 16). An additional RT-PCR primer was designed from a region of identity between the selected cDNA and the SASE data (Table I). A 900 bp RT-PCR clone was obtained using the latter primer in conjunction with a trapped exon derived primer. In total, 4.2 kb of coding sequence was obtained using RT-PCR.

Several cDNAs were cloned using the GeneTrapper direct selection system and oligos designed from the 5' most trapped exon encoding sequences with homology to ABC1 (trapped exon L48747). The longest clone isolated with the GeneTrapper system was 5719 bp in length (ABCgt.1) (Figure 8). This cDNA contains a 792 bp 3' untranslated region with a consensus polyadenylation - cleavage site 20 bp upstream of the polyA tail. An additional cDNA clone (ABC.5) was isolated using a radiolabeled 1.1 kb RT-PCR product (ABC3-12) as a probe (Figure 16). The 5' end of the ABC3 cDNA was further characterized using 5' RACE, with several RACE products containing multiple in-frame stop codons upstream of the start methionine.

Sequence analysis indicated that clone ABCgt.1 lacks 147 bp of sequence found in the RT-PCR clones and the cDNA clone ABC.5. The additional 147 bp segment is likely to be the result of alternative splicing, in that it does

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not interrupt the open reading frame. The presence of both transcript populations has been confirmed by PCR using primers flanking the alternatively spliced exon.

A 6.4 kb cDNA has been assembled for the hABC3 transporter. The assembled cDNA contains a 5116 nucleotide long open reading frame encoding 1705 amino acids, with the predicted protein having a molecular weight of 191 kDa. The proposed start methionine is 50 bp upstream of the 5' end of clone ABCgt.1. Although the sequence surrounding the start methionine matches the Kozak sequence in only 6 of 10 positions (Kozak, *J. Cell Biol.* 115:887-903, 1991), the two positions which have been shown to be critical for function (an A at -3 and a G at +4) are conserved in hABC3. The hABC3 cDNA contains a 792 bp 3' UTR with a consensus polyadenylation/cleavage site 20 bp upstream of the polyA tract.

A 6.8 kb transcript is detected by a 3' UTR cDNA probe on northern blots with highest levels of expression being observed in lung with lesser amounts in brain, heart, and pancreas. Significantly lower levels of expression were observed in placenta and skeletal muscle after longer exposure times. The ABC3 transcript was not detected in either liver or kidney.

RPL3L (SEM L3): The longest cDNA is 1548 nucleotides in length (Figure 11). All three cDNAs have an open reading frame (ORF) of 1224 nucleotide with the longest cDNA containing a 48 nucleotide 5' untranslated region. An inframe stop codon at position 7 is followed by the Kozak initiation sequence CCACC*ATGT* (SEQ ID NO:68) (Kozak, *supra*.). The 3' UTR for each of the three cDNAs vary in length, and lacks a consensus polyadenylation cleavage site.

The longest cDNA was compared to the human, bovine and murine ribosomal L3 genes. At the nucleotide level there is only 74% identity between the RPL3L (SEM L3)

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cDNA and the consensus from these other ribosomal L3 cDNAs. This is in sharp contrast to the 98% identity shared between human, bovine, and murine L3 nucleotide sequences. There is no similarity between the 3' UTR of the cDNAs isolated here and the other L3 genes.

hALR: Sequences were cloned from the human ALR gene by 3' RACE using primers (e.g., external 5'-TGGCCCAGTTCATACATTTA-3' (SEQ ID NO:69) and internal 5'-TTACCCCTGTGAGGAGTGTG-3' (SEQ ID NO:70)) designed from the exon trap. A total of 468 bp have been obtained from the human ALR gene (Figure 13).

Example VII: Amino Acid Sequence Analysis

hNET: hNET cDNA has at least 210 bp of 5' untranslated sequence, a 5' start methionine codon, a 3' stop codon (TGA) and is predicted to be 580 amino acids in length (Figure 4), with the common domain structure of the netrin family being conserved (Figure 20A). Overall, the human netrin was found to have higher homology to chicken netrin-2 than netrin-1, i.e., 56.3% versus 53.9%. As is the case with the other members of the netrin family, the region of greatest conservation includes the three EGF repeats, while the C-terminal domains are less well conserved (Figure 20A). The EGF repeats are 78.7% and 82.2% identical between the human netrin and chicken netrin-1 and netrin-2, respectively, and 66.3% identical when compared to UNC-6. The C-terminal domains of the human netrin and chicken netrin -1 and -2 are 41.9% and 42.5% indentical, respectively with the same domain of UNC-6 being only 29.4% identical to human netrin. Overall, the human netrin more closely resembles the chicken netrins and UNC-6 than *Drosophila* NETA and NETB, since NETA contains an expansion in the C-domain while NETB contains additional sequences in the VI and V-1 domains (Harris *et al.*, 1996, *supra*; Mitchell *et al.*, 1996, *supra*).

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The Structure of the Netrin Genes is Conserved Between Drosophila and Human

The positions of the introns in the human gene were compared to the encoded protein to determine if the overall gene structure of the netrin/UNC-6 family is conserved (Figure 20B). This analysis revealed striking similarities between the *Drosophila* netrin genes and the human netrin gene. In the human gene, exon 1 contains the signal peptide, domain VI and the first EGF domain (domain V-1), while exons two and three each contain an EGF repeat, domains V-2 and V-3, respectively. Exons 4, 5, and 6 contain portions of the C-domain. With the exception of an additional intron in the C-domain, this motif/exon arrangement is conserved in the *Drosophila* netrin genes. The coding regions of the two *Drosophila* netrin genes have been shown to be highly conserved with each being disrupted by six introns that occur in homologous sites (Harris *et al.*, 1996, *supra*). The position of five of the six *Drosophila* introns was found to be conserved in the human gene (Figure 20B). The UNC-6 gene contains 12 introns in the coding region (Ishii *et al.*, 1992, *supra*), the position of five of which correlate with the positions of the introns in the human gene. Interestingly, the sixth *Drosophila* intron that does not have a counterpart in the human gene and is the only intron from *Drosophila* that is not conserved in the UNC-6 gene.

hABC3: Database searches revealed homology between ABC3 and murine ABC1 and ABC2 (Luciani *et al.*, *supra*. 1994). In addition to the murine ABC1 and ABC2 proteins, ABC3 also shows homology to the putative *C. elegans* protein encoded by the cosmid sequence of C48B4.4 (Wilson *et al.*, *supra*.). Overall, ABC3, ABC1, ABC2 and sequences encoded by *C. elegans* cosmid C48B4.4 have highest homology in the regions surrounding the ATP binding cassettes (Figure 17). However, when one compares the sequence between the first ATP binding cassette and the second transmembrane domain, referred to as the linker domain (Luciani *et al.*, *supra*.

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1994), ABC3 shares much lower homology to these same 3 proteins listed above (amino acids 765-1044 in ABC3 in Figure 17). The linker domain of ABC3 is approximately 200 residues shorter than the linker domain present in ABC1 and ABC2. Consequently, an optimum protein alignment positions a gap in the ABC3 sequence immediately C-terminal of a conserved HH1 hydrophobic domain (Luciani *et al., supra.* 1994), located at position 917 through 959 in ABC3 (Figure 17). Additional comparisons indicate that the ABC3 linker domain is nearly identical in size to the linker domain encoded by *C. elegans* cosmid C48B4.4. As is the case with ABC1 and ABC2, the linker domain of ABC3 contains numerous polar residues and several potential phosphorylation sites.

Further analysis of the deduced ABC3 protein sequence revealed additional similarities to the ABC1/ABC2 subfamily. Based on PSORT analysis (Nakai *et al., supra.*), the ABC3 protein does not appear to contain an N-terminal signal sequence and is likely to be a Type III membrane protein (Singer, *Annu. Rev. Cell Biol.* 6:247-296 1990), with sequences N-terminal of the first transmembrane domain being located in the cytoplasm (Figure 17). Similar topography has been described for ABC1 (Luciani *et al., supra.* 1994) and all other ABC transported described to date (Higgins, *supra.* 1992). As mentioned above, murine ABC1 and ABC2 have been shown to contain a novel hydrophobic region, HH1, within the conserved linker domain. Although the HH1 domain is not well conserved at the amino acid level in ABC3, an HH1 domain does appear to be present within the linker region based on hydrophilicity analysis. A similar HH1 domain is also found in sequences encoded by cosmid C48B4.4 from *C. elegans*. In all these cases, the HH1 domain is predicted to have a ß-sheet conformation.

RPL3L (SEM L3): The RPL3L (SEM L3) cDNA open reading frame predicts a 407 amino acid polypeptide of 46.3 kD (Figure 11). *In vitro* transcription - translation of RPL3L (SEM L3) cDNA resulted in a protein product with an

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apparent molecular weight of 46 kD which is in close agreement with the predicted weight of 46.3 kD.

Two nuclear targeting sequences, which are 100% conserved between man, mouse and cow, diverged slightly in the RPL3L (SEM L3) amino acid sequence. The first targeting site is the 21 amino acid N-terminal oligopeptide. The serine and arginine present at positions 13 and 19 respectively, in human, bovine and murine L3 are replaced with histidines in RPL3L (SEM L3) (Figure 12). The second potential nuclear targeting site is the bipartite motif. Here the human, bovine and murine proteins have a KKR-$(aa)_{12}$-KRR at position 341-358 while the SEM L3 gene has KKR-$(aa)_{10}$-HHSRQ at position 341-358. The second half of this bipartite motif, while remaining basic, does not match those found in other nuclear targeting motifs (Simonic *et al.*, *supra.* 1994). Overall, there is 77.2% amino acid identity between the RPL3L (SEM L3) and the consensus from the other mammalian L3 ribosomal genes, with 56% of the nucleotide differences between RPL3L (SEM L3) and the human L3 being silent.

hALR: hALR cDNA sequences encode a 119 amino acid protein which is 84.8% identical and 94.1% similar to the rat ALR protein (see, Figures 13 and 14).

Although the invention has been described with reference to the disclosed embodiments, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the claims which follow the Sequence Listing.

BNSDOCID: <WO__9748797A1_I_>

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: GENZYME CORPORATION

(ii) TITLE OF INVENTION: NOVEL HUMAN CHROMOSOME 16 GENES, COMPOSITIONS, METHODS OF MAKING AND USING SAME

(iii) NUMBER OF SEQUENCES: 83

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: GENZYME CORPORATION
(B) STREET: One Mountain Road
(C) CITY: Framingham
(D) STATE: Massachusetts
(E) COUNTRY: United States of America
(F) ZIP: 01701

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE: 16-JAN-1997
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/665,259
(B) FILING DATE: 17-JUN-1996

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/720,614
(B) FILING DATE: 01-OCT-1996

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/762,500
(B) FILING DATE: 09-DEC-1996

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: PCT/US96/10469
(B) FILING DATE: 17-JUN-1996

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Dugan, Deborah A.
(B) REGISTRATION NUMBER: 37,315
(C) REFERENCE/DOCKET NUMBER: IG5-9.4

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (508) 872-8400
(B) TELEFAX: (508) 872-5415

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 179 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

BNSDOCID: <WO___9748797A1_I_>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
Leu His Leu Glu Gly Pro Phe Ile Ser Arg Glu Lys Arg Gly Thr His
1               5                  10                  15

Pro Glu Ala His Leu Arg Ser Phe Glu Ala Asp Ala Phe Gln Asp Leu
            20                  25                  30

Leu Ala Thr Tyr Gly Pro Leu Asp Asn Val Arg Ile Val Thr Leu Asp
        35                  40                  45

Pro Glu Leu Gly Arg Ser His Glu Val Phe Arg Thr Leu Thr Xaa Arg
    50                  55                  60

Ser Ile Cys Val Ser Leu Gly His Ser Val Ala Asp Leu Arg Ala Ala
65                  70                  75                  80

Glu Asp Ala Val Trp Ser Gly Ala Thr Phe Ile Thr His Leu Phe Asn
                85                  90                  95

Ala Met Leu Pro Phe His His Arg Asp Pro Gly Ile Val Gly Leu Leu
            100                 105                 110

Thr Ser Asp Arg Pro Ala Gly Arg Cys Ile Phe Tyr Gly Met Ile Ala
        115                 120                 125

Asp Gly Thr His Thr Asn Pro Ala Ala Leu Arg Ile Ala His Arg Ala
    130                 135                 140

His Pro Gln Gly Leu Val Leu Val Thr Asp Ala Ile Pro Ala Leu Gly
145                 150                 155                 160

Leu Gly Asn Gly Arg His Thr Leu Gly Gln Gln Glu Val Glu Val Asp
                165                 170                 175

Gly Leu Thr
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 90 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
His Leu Glu Gly Pro Phe Ile Ser Lys Arg Gly His Pro Glu Ser Tyr
1               5                  10                  15

Gly Asn Ile Val Thr Pro Glu Leu Glu Val Ser Gly His Ser Ala Leu
            20                  25                  30

Glu Ala Val Ser Gly Ala Ile Thr His Leu Phe Asn Ala Met His His
        35                  40                  45

Arg Asp Pro Gly Gly Leu Leu Thr Ser Leu Tyr Gly Ile Asp Gly His
    50                  55                  60
```


BNSDOCID: <WO___9748797A1_I_>

Thr Ala Leu Arg Ile Ala Gly Leu Val Leu Val Thr Asp Ala Ile Ala
65 70 75 80

Leu Gly Gly His Leu Gly Gln Val Gly Leu
85 90

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 64 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Leu His Leu Glu Gly Pro Lys Gly Thr His Arg Ala Ala Asp Leu Asp
1 5 10 15

Val Thr Leu Pro Glu Glu Val Leu Ile Val Ser Gly His Ser Ala Leu
20 25 30

Ala Gly Thr Phe Thr His Leu Asn Ala Met Pro Gly Leu Leu Ile Gly
35 40 45

Ile Ala Asp Gly His Ala Arg Ala Arg Leu Leu Val Thr Asp Ala Gly
50 55 60

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 55 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Leu His Glu Pro Ser Glu Lys Gly His Arg Asp Leu Gly Asp Thr Glu
1 5 10 15

Ile Val Ser Gly His Ser Ala Ala Ala Gly Ala Thr Phe Thr His Leu
20 25 30

Asn Ala Met Pro Gly Gly Ile Asp Gly His Asn Arg Ile Leu Val Thr
35 40 45

Asp Ile Ala Gly Leu Gly Thr
50 55

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 amino acids
(B) TYPE: amino acid

BNSDOCID: <WO___9748797A1_I_>

(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Cys Asp Cys His Pro Val Gly Ala Ala Gly Lys Thr Cys Asn Gln Thr
1 5 10 15

Thr Gly Gln Cys Pro Cys Lys Asp Gly Val Thr Gly Leu Thr Cys Asn
20 25 30

Arg Cys Ala Pro Gly Phe Gln Gln Ser Arg Ser Pro Val Ala Pro Cys
35 40 45

Val

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Cys Asp Cys His Pro Val Gly Ala Ala Gly Lys Thr Cys Asn Gln Thr
1 5 10 15

Thr Gly Gln Cys Pro Cys Lys Asp Gly Val Thr Gly Leu Thr Cys Asn
20 25 30

Arg Cys Ala Pro Gly Phe Gln Gln Ser Arg Ser Pro Val Ala Pro Cys
35 40 45

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

BNSDOCID: <WO___9748797A1_I_>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Cys Asp Cys His Pro Val Gly Ala Ala Gly Thr Cys Asn Gln Thr Thr
1 5 10 15

Gly Gln Cys Pro Cys Lys Asp Gly Val Thr Gly Thr Cys Asn Arg Cys
20 25 30

Ala Lys Gly Gln Gln Ser Arg Ser Pro Ala Pro Cys
35 40

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Cys Cys His Pro Val Gly Gly Cys Asn Gln Gly Gln Cys Cys Lys Gly
1 5 10 15

Val Thr Gly Thr Cys Asn Arg Cys Ala Lys Gly Gln Gln Ser Arg Ser
20 25 30

Val Pro Cys
35

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

His Ser Pro Ser Leu Ser Ala Glu Thr Pro Ile Pro Gly Pro Thr Glu
1 5 10 15

Asp Ser Ser Pro Val Gln Pro Gln Asp Cys Asp Ser His Cys Lys Pro
20 25 30

Ala Arg Gly Ser Tyr Arg Ile Ser Leu Lys Lys Phe Cys Lys Lys Asp
35 40 45

Tyr

BNSDOCID: <WO___9748797A1_I_>

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Ile Ser Pro Asp Cys Asp Ser Cys Lys Pro Ala Gly Tyr Ile Lys Lys
1 5 10 15

Cys Lys Lys Asp Tyr
20

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Pro Pro Thr Ser Ser Pro Asp Cys Asp Ser Cys Lys Gly Ile Lys Lys
1 5 10 15

Cys Lys Lys Asp Tyr
20

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 88 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Leu Val Gly Asp Ser Gly Val Gly Lys Thr Cys Leu Leu Val Arg
1 5 10 15

Phe Lys Asp Gly Ala Phe Leu Ala Gly Thr Phe Ile Ser Thr Val Gly
20 25 30

Ile Asp Phe Arg Asn Lys Val Leu Asp Val Asp Gly Val Lys Ala Lys
35 40 45

BNSDOCID: <WO___9748797A1_I_>

Leu Gln Met Trp Asp Thr Ala Gly Gln Glu Arg Phe Arg Ser Val Thr
50 55 60

His Ala Tyr Tyr Arg Asp Ala His Ala Leu Leu Leu Tyr Asp Val
65 70 75 80

Thr Asn Lys Ala Ser Phe Asp Asn
85

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 83 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Met Leu Val Gly Asp Ser Gly Val Gly Lys Thr Cys Leu Leu Val Arg
1 5 10 15

Phe Lys Asp Gly Ala Phe Leu Ala Gly Thr Phe Ile Ser Thr Val Gly
20 25 30

Ile Asp Phe Arg Asn Lys Val Leu Asp Val Asp Gly Lys Lys Leu Gln
35 40 45

Trp Asp Thr Ala Gly Gln Glu Arg Phe Arg Ser Val Thr His Ala Tyr
50 55 60

Tyr Arg Asp Ala His Ala Leu Leu Leu Leu Tyr Asp Thr Asn Lys Ser
65 70 75 80

Phe Asp Asn

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 83 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Phe Gln Asn His Phe Glu Pro Gly Val Tyr Val Cys Ala Lys Cys Gly
1 5 10 15

Tyr Glu Leu Phe Ser Ser Arg Ser Lys Tyr Ala His Ser Ser Pro Trp
20 25 30

Pro Ala Phe Thr Glu Thr Ile His Ala Asp Ser Val Ala Lys Arg Pro
35 40 45

BNSDOCID: <WO___9748797A1_I_>

Glu His Asn Arg Ser Glu Ala Leu Lys Val Ser Cys Gly Lys Cys Gly
50 55 60

Asn Gly Leu Gly His Glu Phe Leu Asn Asp Gly Pro Lys Pro Gly Gln
65 70 75 80

Ser Arg Phe

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Phe Pro Gly Tyr Val Gly Leu Phe Ser Ser Lys Tyr Trp Pro Phe Thr
1 5 10 15

Ile Ala Ser Val Val Leu Gly His Phe Asp Gly Pro
20 25

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Glu Gly Val Tyr Cys Ala Cys Asp Leu Ser Ser Lys Trp Pro Ala Phe
1 5 10 15

Glu Ala Cys Cys Leu Gly His Phe Gly Lys
20 25

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

BNSDOCID: <WO___9748797A1_I_>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Phe His Phe Glu Gly Tyr Val Cys Cys Gly Glu Leu Phe Ser Lys Trp
1 5 10 15

Pro Ala Phe Glu Val Cys Cys Leu Gly His Phe Asn Asp Gly Pro Lys
20 25 30

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Phe Gly Tyr Val Gly Phe Ser Ser Lys Trp Pro Phe Thr Ile Asp Val
1 5 10 15

Gly Asn Leu Gly His Phe Asp Gly Pro Lys Gly Arg
20 25

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6803 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GGAGCTCGGT TGGAAACCCC CCGAGGCATA ATAGGCGCTC GATAAATGTG CAATAGGTGA 60

ACATGTGGTG GCTTGCAGGC GTCTGGGGGG AGACAGCAGG TTCTGGGCTG GGCAGGGAAT 120

TATTGGATCA ACGGGCATCT TACAGGAAAG ACTCTCAGCT CCCTGCCGCC TAGGACTGTC 180

CAGCCCATCT ATGCCCTCTC CCCAGCCTGT GCCCCAAAGC TGGAGCTGCC ACTCTAGGGG 240

TGAGGGGTGG GGTGGGGAGG GGGAGGCGAA GCACTGCGGC CTGAGTTGCA GGTGGGGGGA 300

GGGGAGGCGG AGCTTCTTTG TTGCAGAAGG TGCCAGGAGG GGGCAGGGCC AGTGGAGAGG 360

TGGGAGGTGG GAGAGGCCCC AGCCAGGGGC TGGGACAGGT GGCTGGGTCC CTGGGGAGCA 420

ATAAGTCCCG CTTGGGCGCT GTGGGGAGGC CCTTCCTAAC TCCCAAACAC CATCTGTGAG 480

GGCTGGGGGT GGGGGCAGAG TAGCGTGTGC AGAGGACTGT TCCTGGGGAG AGGCCCTGTG 540

ACCAGCGGCC TCCTCCCTGG GGAGCTGGCG GTACAATGGC CCTCTGGGCC CACGGCCTCC 600

BNSDOCID: <WO___9748797A1_I_>

CGCCGCTGCT GCTGACCCAG ATGAACAATT GGGGCAGGGC TGAGCCCCAG GCACCTACTT 660

TCCCCCACCC CAGAAGCCAC CAGACGTTCT GCAGACCCCA GTCCTGGCTC ACAGGGAAGC 720

TGAGCTGGAG ACAAAGCCAG CCCCTCTGAT GAGGGTGGAA GAGGCTGCTG GCCACTGTCC 780

CTCTTGCAGC CTGGCTGGCA GCCAGTCTGG CAGTGGCCCT GACGTCCAGA GACAGCTTGG 840

GTTTCCCCAG AGGCTTGTCT CTGGCCAGTG GGACCCCTCT GTCAGGCCTG GGCTTTTCTC 900

TCCACTGTCC CAGAATGATG ATCTCAGCCC CCATAGTCCC CCCAGGGTTC CTCCCACCCT 960

TAGGGTGGGG TGTCGGGGGG TGGGGGTTGG GAGCCAGAAG GACCTTGAAG AGGGTGGTTG 1020

GGACGTTTCA GGTTCTAAGC TTGACCCACA GAGCGGAGCG TGAGCCCCGT CAGGTTGAGG 1080

TCCCTCAACT TGTAAAGGAC ACAATTCCAT TCTCTTTATC AGGAAGCTGA GGGGCAGGGG 1140

CCCTGTGGCA GAGAGAGAGC CCCTTAGCCC TCTCTGTTCA GTCCTCCGGT GCCCCCATCC 1200

CTGTGCATCT GTGGCTGTCA CATGCAGATG TGTGGCAAGG AGAAGGTGCC CACCAGCCAG 1260

TGTCAGTTGC TCCAGGAGCC AAGCCAGGTG CCCTATCACC CTGTCTTCCC GTTCCTCCCC 1320

TCCATGGTCA GGCCCTCCTG CTCCCTCCTC TGGTCCTTCA GTTTCCCCTA GGAGGCTTCC 1380

GTGTCCTCCT GCCCCTCCTC TCCCCAACAG CGGGATGCGT CTACCTCTCC ATTCTCTTCC 1440

TCCTGGTCCT TGCTCATCTC TGGTCGTGTC CAGGGTAGCA CCCACGTGGC CTCCTCCACC 1500

AGCTGCAGGC CTGGCCTCCC ATCTGAAACG GGGCATTCAG GCCTCGATGC TGGCCCTGCA 1560

CGGAACTTGT TCCCTGCCCC TCCCTGGGAT GCTTGGCCTC CTCTGTCAAG GACCTGAAAG 1620

TCGGAGGGGA GGAGGTTTCT CTGACCAGAG CTGTTCCTGG ACCCTCTTTG GTGGTGTCGC 1680

TCCCAGGCAC AGCTACCCCA TCCCCAGCTA GTCCCCAGGC CACCCAGCTG GGCTTCTGCC 1740

TCAGTTTCCC TGCCCAAACG TGCTGTGACG TAGGGCAGTG GGCTCCGGGT TGCGACCAGC 1800

CCCTTCCCAT GATTAAACCC TACTCCCTGC CCCTGCAGAG GGGTCCTCAA CAGCTAACCA 1860

AGCCCCCGAA CCCCAAGAAG CCACCCCATC CCACCCTCCA GCTTCCATGT CCTCCCTGCC 1920

AGCTGGGCCC GTGGCAGAGG TGCCCCTAGA AACTTGCAGA CCCAGGGAGC TTTGGGATCA 1980

GAATCTGGCC TGGTGCAGGG GATGCTGGCC TCATGTCTTA GCCCAGCTCA GGCCCATGGG 2040

GGTGCCCCCC TTCCTCAACA TGGGCAGGAG ACACTCCAAT TTGTGCAGCT CTCGACTTGG 2100

GCCTGATGCC ACTTGAGACT CATCAAATCC AACAGCTTCA GAGCGCGTGC TGAGTAACAG 2160

GCATCTGGCA GGTGAGGAAA CAGGAGCCCA AGACATGCAG CCAGAAATGG GGCAGTTGGA 2220

TTCAAAATTA GACCTGACCG AATCCTGGGT TCCTTCTACT CGAGTAGATG CTGCTTTGGG 2280

GATGACCCTT CAACTGGTGG TTACTTGGCT TCCCTACCTG GGGAACATCC AGGGCCTCTG 2340

CTGTCAGACC CGGGGCCTTG CCTGCCTGAT GGTCTTCAGG GAGGAGGCGA CCCAGACCCC 2400

CGTCCAGCAC GTGGCACAGC CCCAGGAGCA GTAAAGACCT GGCTGTGGGC CCAGGACCCT 2460

GCTGGGTGGT CCCCCACGGG CTGCGAAGGC TGAGCTGCCC CCGTCCAGAC CCCTCCCGCC 2520

AGCGCATTCC TGGCTCCCCG GCCCCTCCCC TGGCTCCCGG GCCTCCCAGC CCCCTTCCCC 2580

BNSDOCID: <WO___9748797A1_I_>

GCTGGCCCAG CCCGCGTCTG AATCTGCTTC TGATTCCAGC TCTGCGATGA GGCCCCCTCC 2640

CCTCCCCTGC GTCCTTCCCG ACCCGAGCAG CCCCGCCCCC GGCTGGGCCC GGGCTTGCGC 2700

CTGCTGCGCC CCCCACCCCC TCCTGGCACA GCTCGTCCGC CCTCGCTGCA GCCGGGAGGA 2760

GGCGGCGGCC CGTGCACCGC AGGCCCCGCC CGCCCACGGC CCTTCCCGGG AGGCCGGGAG 2820

ACCTGCTCCG CCCGGCCCTC GGTGGGTGAG TGCGAGCGGC GGGTGGGGCC TCCGCGGGCG 2880

GAGGCACCGG GAGCGGGGGC GACGCCTGTC ATCGCTCTAG GCCCAGCGGG AGGACGCGCC 2940

AACATCCCCG CTGCTGTGCT GGGCCCGGGG CGTGCCCGCC GCTGCTCCCA CCTCTGGGCC 3000

GGGCTGGGGC CGCCCGGGGG CCCTGTTCCT CGGCATTGCG GGCCTGGTGG GCAGAGCCGC 3060

GGAGAGGGCT TCTTTTCCCC AAGGGCAGCG TCTTGGGGCC CGGCCACTGG CTGACCCGCA 3120

GCGGCTCCGG CCATGCCTGG CTGGCCCTGG GGGCTGCTGC TGACGGCAGG CACGCTCTTC 3180

GCCGCCCTGA GTCCTGGGCC GCCGGCGCCC GCCGACCCCT GCCACGATGA GGGGGGTGCG 3240

CCCCGCGGCT GCGTGCCAGG ACTGGTGAAC GCCGCCCTGG GCCGCGAGGT GCTGGCTTCC 3300

AGCACGTGCG GGCGGCCGGC CACTCGGGCC TGCGACGCCT CCGACCCGCG ACGGGCACAC 3360

TCCCCCGCCC TCCTTACTTC CCCAGGGGGC ACGGCCAGCC CTCTGTGCTG GCGCTCGGAG 3420

TCCCTGCCTC GGGCGCCCCT CAACGTGACT CTCACGGTGC CCCTGGGCAA GGCTTTTGAG 3480

CTGGTCTTCG TGAGCCTGCG CTTCTGCTCA GCTCCCCCAG CCTCCGTGGC CCTGCTCAAG 3540

TCTCAGGACC ATGGCCGCAG CTGGGCCCCG CTGGGCTTCT TCTCCTCCCA CTGTGACCTG 3600

GACTATGGCC GTCTGCCTGC CCCTGCCAAT GGCCCAGCTG GCCCAGGGCC TGAGGCCCTG 3660

TGCTTCCCCG CACCCCTGGC CCAGCCTGAT GGCAGCGGCC TTCTGGCCTT CAGCATGCAG 3720

GACAGCAGCC CCCCAGGCCT GGACCTGGAC AGCAGCCCAG TGCTCCAAGA CTGGGTGACC 3780

GCCACCGACG TCCGTGTAGT GCTCACAAGG CCTAGCACGG CAGGTGACCC CAGGGACATG 3840

GAGGCCGTCG TCCCTTACTC CTACGCAGCC ACCGACCTCC AGGTGGGCGG GCGCTGCAAG 3900

TGCAATGGAC ATGCCTCACG GTGCCTGCTG GACACACAGG GCCACCTGAT CTGCGACTGT 3960

CGGCATGGCA CCGAGGGCCC TGACTGCGGC CGCTGCAAGC CCTTCTACTG CGACAGGCCA 4020

TGGCAGCGGG CCACTGCCCG GGAATCCCAC GCCTGCCTCG GTGAGGCCTT GGAGGGTGGC 4080

CTGGGGACCT TGGACACAAC CAGCCTGCCC CTGACCCATC CCTCCCTGCA GCTTGCTCCT 4140

GCAACGGCCA TGCCCGCCGC TGCCGCTTCA ACATGGAGCT GTACCGACTG TCCGGCCGCC 4200

GCAGCGGGGG TGTCTGTCTC AACTGCCGGC ACAACACCGC CGGCCGCCAC TGCCACTACT 4260

GCCGGGAGGG CTTCTATCGA GACCCTGGCC GTGCCCTGAG TGACCGTCGG GCTTGCAGGG 4320

GTGAGCCACC ACCGGCCACC TGCAGGCCCT CACCCTCTGA CTTCCCAGAT CCCCAGACAG 4380

GCTTCTGACC AGGCCCTTCC CACCTCTGTC CTCAGCCTGC GACTGTCACC CGGTTGGTGC 4440

TGCTGGCAAG ACCTGCAACC AGACCACAGG CCAGTGTCCC TGCAAGGATG GCGTCACTGG 4500

CCTCACCTGC AACCGCTGCG CGCCTGGCTT CCAGCAAAGC CGCTCCCCAG TGGCGCCCTG 4560

SUBSTITUTE SHEET (RULE 26)

BNSDOCID: <WO___9748797A1_I_>

TGTTAGTGAG TGACCCTGCC CCGCCTCAGC CACCAAGCCA AGGCCACCCC AGCTCCCTGC 4620

TGTTGTCCCG TCTATTCCCC GAGCCCTGCA GATCTCTCTG CCCCTCCATC GCAGGCCATT 4680

CTCCCTCCCT CTCTGCAGAG ACCCCTATCC CTGGACCCAC TGAGGACAGC AGCCCTGTGC 4740

AGCCCCAGGG TGAGTGGACA CAGGACAGGG CCCCAGACTG GCATGACTTT GGGGGAGGGG 4800

GCTCTGGGAG GAGAGGGTGG GGAAAGGGAG TCTGTGCCAG CCTCCCACCT TCTACCCAGA 4860

CTGTGACTCG CACTGCAAAC CTGCCCGTGG CAGCTACCGC ATCAGCCTAA AGAAGTTCTG 4920

CAAGAAGGAC TATGGTAGGT GCCCTCAGGC CTCCCGCGGA CCTTCCCACC TTCCTCCTCT 4980

CCCTACCTTC CCTCCTCCGC CAGCTTCCCC TTGGAACGCC TTGACCCTTG CTGGGCCCCA 5040

AGGCCCATCC TCATCCCTCA GGTCCTCCAC GGGCAGCGAC CCCGCCCCTT CAGCCCCCAC 5100

TGCCCTCCTG GTGTCCTCCC CGTGCCTCCC CCTACCGCGG GCAGGCCGCC CCTTCCTGAC 5160

CCCGCCCCCT CTCGCTCTCC CCGCAGCGGT GCAGGTGGCG GTGGGTGCGC GCGGCGAGGC 5220

GCGCGGCGCG TGGACACGCT TCCCGGTGGC GGTGCTCGCC GTGTTCCGGA GCGGAGAGGA 5280

GCGCGCGCGG CGCGGGAGTA GCGCGCTGTG GGTGCCCGCC GGGGATGCGG CCTGCGGCTG 5340

CCCGCGCCTG CTCCCCGGCC GCCGCTACCT CCTGCTGGGG GGCGGGCCTG GAGCCGCGGC 5400

TGGGGGCGCG GGGGGCCGGG GGCCCGGGCT CATCGCCGCC CGCGGAAGCC TCGTGCTACC 5460

CTGGAGGGAC GCGTGGACGC GGCGCCTGCG GAGGCTGCAG CGACGCGAAC GGCGGGGGCG 5520

CTGCAGCGCC GCCTGAGCCC GCCGGCTGGG CAGGGCGGCC GCTGCTCCCA CATCTAGGCG 5580

CACGTTCACC CTGTGCCTTC GCCTGCCAAG GAGTCCTTGC TCGCGTCGCG CGTGTCGCCA 5640

CCTGGGCCGC CGCCCCGTCC CCGCCGGCAG CTCCCTCGGT ACCTCCCGTC TGGCCCTGGG 5700

GGGATGTGAC CGGCGCACGG ACAGCCCGCC CCGCACAGAG GCAGATGATA TGGCACACCC 5760

GGAGGACCCC ATGGTCTCCC GCCCTCTGGC TGTCGGCCCT GTCCCAGGGG CACTGGGATA 5820

CCCGGAAGGC TGTGAATCCT TCGTGATGCC GGGCCCTCTC GGGGATCTCA GATCATCCCC 5880

GGGGCCGCTG TGATGCACCC CCACCTGTGC GGCGACCCGC CAGGAGCGCA CTGACCTCCC 5940

CAAAGACTGT GGCCACCGCA GGCGCCTTGG ACCCCCATGG GGGACAGGGC GTCCCCTGCC 6000

TCCTGCAGCC CCACGAGGGC GGCGGCCTTG GCCCTGCGGC TGGGCGTCCG CGTCCGGGCG 6060

CCCCGCGGCG TCTGCTGCCG GGTCCCGTAA CTTTCTTGGC CGCCTGTGTC CCCGTCTGCC 6120

GGCTCCGTCC GGCCGTCCCT CTCTCTGCCG CGTCTCTGAC CCTCGGCGCC ACAGCTCCTC 6180

AGCTCAGGGC CCGTCCCAGA ACCTCCTTCC AGCCCTTCTC CCCCGACTCG GGAAGGGACG 6240

TCGTGCCCAC GCGGTTCCGG ATCCACGCGT GACCCGGCCG GACCGCGACT CCGACAGGCG 6300

GCTGTCCGGG CCCCCGATGC CCTCGGCAGG GCCGTGCCAC CCCCCGCCCC TTGTTGTCCC 6360

CCCGGGACCG GCACTGCCGT TTGCCTCCTC TCCGCACGGG ACCGGTTCCC GGCCGGCCCC 6420

AGCTTCCGCC GCTGCGGCCG CCGACCGTCA GCGCGCATGC CCAGAGCCGG GCAGGCCGGA 6480

GCCCCGCCGG CTCTCCGGGG TGGGCACAGG GCGACAGCTC GGCGGGGGCG GGGCCGAGCA 6540

SUBSTITUTE SHEET (RULE 26)

BNSDOCID: <WO___9748797A1_I_>

CGCGCGTGCG CAGAAAGGCC GGCGCGGCAG GCTGAGGAGA AAGCGGCGCG CGGAGGTGGG 6600

TGCGCTCGGG GCGTGCGGGG GGCGCGCGGC GGGGTGGCGG GTGGCGGGGC CGGGTCCCCG 6660

CTGTCACCGC GGTCGGCGCG TGCTGGGGGC GGGAGCGTGG GGGCCGGGCT GCGTGCCCCA 6720

TTCGAGGCGG GGATCCCCGG CCACGCGCGG GTTGGGGGCT CCAGAGCCCG GCACCGCCCG 6780

GCGCTGCAGC TGCGGCTTGG CCT 6803

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1743 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1740

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
ATG CCT GGC TGG CCC TGG GGG CTG CTG CTG ACG GCA GGC ACG CTC TTC      48
Met Pro Gly Trp Pro Trp Gly Leu Leu Leu Thr Ala Gly Thr Leu Phe
 1               5                  10                  15

GCC GCC CTG AGT CCT GGG CCG CCG GCG CCC GCC GAC CCC TGC CAC GAT      96
Ala Ala Leu Ser Pro Gly Pro Pro Ala Pro Ala Asp Pro Cys His Asp
            20                  25                  30

GAG GGG GGT GCG CCC CGC GGC TGC GTG CCA GGA CTG GTG AAC GCC GCC     144
Glu Gly Gly Ala Pro Arg Gly Cys Val Pro Gly Leu Val Asn Ala Ala
        35                  40                  45

CTG GGC CGC GAG GTG CTG GCT TCC AGC ACG TGC GGG CGG CCG GCC ACT     192
Leu Gly Arg Glu Val Leu Ala Ser Ser Thr Cys Gly Arg Pro Ala Thr
    50                  55                  60

CGG GCC TGC GAC GCC TCC GAC CCG CGA CGG GCA CAC TCC CCC GCC CTC     240
Arg Ala Cys Asp Ala Ser Asp Pro Arg Arg Ala His Ser Pro Ala Leu
65                  70                  75                  80

CTT ACT TCC CCA GGG GGC ACG GCC AGC CCT CTG TGC TGG CGC TCG GAG     288
Leu Thr Ser Pro Gly Gly Thr Ala Ser Pro Leu Cys Trp Arg Ser Glu
                85                  90                  95

TCC CTG CCT CGG GCG CCC CTC AAC GTG ACT CTC ACG GTG CCC CTG GGC     336
Ser Leu Pro Arg Ala Pro Leu Asn Val Thr Leu Thr Val Pro Leu Gly
            100                 105                 110

AAG GCT TTT GAG CTG GTC TTC GTG AGC CTG CGC TTC TGC TCA GCT CCC     384
Lys Ala Phe Glu Leu Val Phe Val Ser Leu Arg Phe Cys Ser Ala Pro
        115                 120                 125

CCA GCC TCC GTG GCC CTG CTC AAG TCT CAG GAC CAT GGC CGC AGC TGG     432
Pro Ala Ser Val Ala Leu Leu Lys Ser Gln Asp His Gly Arg Ser Trp
    130                 135                 140
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BNSDOCID: <WO___9748797A1_I_>

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GCC CCG CTG GGC TTC TTC TCC TCC CAC TGT GAC CTG GAC TAT GGC CGT        480
Ala Pro Leu Gly Phe Phe Ser Ser His Cys Asp Leu Asp Tyr Gly Arg
145                 150                 155                 160

CTG CCT GCC CCT GCC AAT GGC CCA GCT GGC CCA GGG CCT GAG GCC CTG        528
Leu Pro Ala Pro Ala Asn Gly Pro Ala Gly Pro Gly Pro Glu Ala Leu
                165                 170                 175

TGC TTC CCC GCA CCC CTG GCC CAG CCT GAT GGC AGC GGC CTT CTG GCC        576
Cys Phe Pro Ala Pro Leu Ala Gln Pro Asp Gly Ser Gly Leu Leu Ala
            180                 185                 190

TTC AGC ATG CAG GAC AGC AGC CCC CCA GGC CTG GAC CTG GAC AGC AGC        624
Phe Ser Met Gln Asp Ser Ser Pro Pro Gly Leu Asp Leu Asp Ser Ser
        195                 200                 205

CCA GTG CTC CAA GAC TGG GTG ACC GCC ACC GAC GTC CGT GTA GTG CTC        672
Pro Val Leu Gln Asp Trp Val Thr Ala Thr Asp Val Arg Val Val Leu
    210                 215                 220

ACA AGG CCT AGC ACG GCA GGT GAC CCC AGG GAC ATG GAG GCC GTC GTC        720
Thr Arg Pro Ser Thr Ala Gly Asp Pro Arg Asp Met Glu Ala Val Val
225                 230                 235                 240

CCT TAC TCC TAC GCA GCC ACC GAC CTC CAG GTG GGC GGG CGC TGC AAG        768
Pro Tyr Ser Tyr Ala Ala Thr Asp Leu Gln Val Gly Gly Arg Cys Lys
                245                 250                 255

TGC AAT GGA CAT GCC TCA CGG TGC CTG CTG GAC ACA CAG GGC CAC CTG        816
Cys Asn Gly His Ala Ser Arg Cys Leu Leu Asp Thr Gln Gly His Leu
            260                 265                 270

ATC TGC GAC TGT CGG CAT GGC ACC GAG GGC CCT GAC TGC GGC CGC TGC        864
Ile Cys Asp Cys Arg His Gly Thr Glu Gly Pro Asp Cys Gly Arg Cys
        275                 280                 285

AAG CCC TTC TAC TGC GAC AGG CCA TGG CAG CGG GCC ACT GCC CGG GAA        912
Lys Pro Phe Tyr Cys Asp Arg Pro Trp Gln Arg Ala Thr Ala Arg Glu
    290                 295                 300

TCC CAC GCC TGC CTC GCT TGC TCC TGC AAC GGC CAT GCC CGC CGC TGC        960
Ser His Ala Cys Leu Ala Cys Ser Cys Asn Gly His Ala Arg Arg Cys
305                 310                 315                 320

CGC TTC AAC ATG GAG CTG TAC CGA CTG TCC GGC CGC CGC AGC GGG GGT       1008
Arg Phe Asn Met Glu Leu Tyr Arg Leu Ser Gly Arg Arg Ser Gly Gly
                325                 330                 335

GTC TGT CTC AAC TGC CGG CAC AAC ACC GCC GGC CGC CAC TGC CAC TAC       1056
Val Cys Leu Asn Cys Arg His Asn Thr Ala Gly Arg His Cys His Tyr
            340                 345                 350

TGC CGG GAG GGC TTC TAT CGA GAC CCT GGC CGT GCC CTG AGT GAC CGT       1104
Cys Arg Glu Gly Phe Tyr Arg Asp Pro Gly Arg Ala Leu Ser Asp Arg
        355                 360                 365

CGG GCT TGC AGG GCC TGC GAC TGT CAC CCG GTT GGT GCT GCT GGC AAG       1152
Arg Ala Cys Arg Ala Cys Asp Cys His Pro Val Gly Ala Ala Gly Lys
    370                 375                 380

ACC TGC AAC CAG ACC ACA GGC CAG TGT CCC TGC AAG GAT GGC GTC ACT       1200
Thr Cys Asn Gln Thr Thr Gly Gln Cys Pro Cys Lys Asp Gly Val Thr
385                 390                 395                 400
```


BNSDOCID: <WO___9748797A1_I_>

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GGC CTC ACC TGC AAC CGC TGC GCG CCT GGC TTC CAG CAA AGC CGC TCC      1248
Gly Leu Thr Cys Asn Arg Cys Ala Pro Gly Phe Gln Gln Ser Arg Ser
                405                 410                 415

CCA GTG GCG CCC TGT GTT AAG ACC CCT ATC CCT GGA CCC ACT GAG GAC      1296
Pro Val Ala Pro Cys Val Lys Thr Pro Ile Pro Gly Pro Thr Glu Asp
            420                 425                 430

AGC AGC CCT GTG CAG CCC CAG GAC TGT GAC TCG CAC TGC AAA CCT GCC      1344
Ser Ser Pro Val Gln Pro Gln Asp Cys Asp Ser His Cys Lys Pro Ala
        435                 440                 445

CGT GGC AGC TAC CGC ATC AGC CTA AAG AAG TTC TGC AAG AAG GAC TAT      1392
Arg Gly Ser Tyr Arg Ile Ser Leu Lys Lys Phe Cys Lys Lys Asp Tyr
    450                 455                 460

GCG GTG CAG GTG GCG GTG GGT GCG CGC GGC GAG GCG CGC GGC GCG TGG      1440
Ala Val Gln Val Ala Val Gly Ala Arg Gly Glu Ala Arg Gly Ala Trp
465                 470                 475                 480

ACA CGC TTC CCG GTG GCG GTG CTC GCC GTG TTC CGG AGC GGA GAG GAG      1488
Thr Arg Phe Pro Val Ala Val Leu Ala Val Phe Arg Ser Gly Glu Glu
                485                 490                 495

CGC GCG CGG CGC GGG AGT AGC GCG CTG TGG GTG CCC GCC GGG GAT GCG      1536
Arg Ala Arg Arg Gly Ser Ser Ala Leu Trp Val Pro Ala Gly Asp Ala
            500                 505                 510

GCC TGC GGC TGC CCG CGC CTG CTC CCC GGC CGC CGC TAC CTC CTG CTG      1584
Ala Cys Gly Cys Pro Arg Leu Leu Pro Gly Arg Arg Tyr Leu Leu Leu
        515                 520                 525

GGG GGC GGG CCT GGA GCC GCG GCT GGG GGC GCG GGG GGC CGG GGG CCC      1632
Gly Gly Gly Pro Gly Ala Ala Ala Gly Gly Ala Gly Gly Arg Gly Pro
    530                 535                 540

GGG CTC ATC GCC GCC CGC GGA AGC CTC GTG CTA CCC TGG AGG GAC GCG      1680
Gly Leu Ile Ala Ala Arg Gly Ser Leu Val Leu Pro Trp Arg Asp Ala
545                 550                 555                 560

TGG ACG CGG CGC CTG CGG AGG CTG CAG CGA CGC GAA CGG CGG GGG CGC      1728
Trp Thr Arg Arg Leu Arg Arg Leu Gln Arg Arg Glu Arg Arg Gly Arg
                565                 570                 575

TGC AGC GCC GCC TGA                                                 1743
Cys Ser Ala Ala
            580
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 580 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

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Met Pro Gly Trp Pro Trp Gly Leu Leu Leu Thr Ala Gly Thr Leu Phe
  1               5                  10                  15

Ala Ala Leu Ser Pro Gly Pro Pro Ala Pro Ala Asp Pro Cys His Asp
            20                  25                  30
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BNSDOCID: <WO___9748797A1_I_>

Glu Gly Gly Ala Pro Arg Gly Cys Val Pro Gly Leu Val Asn Ala Ala
35 40 45

Leu Gly Arg Glu Val Leu Ala Ser Ser Thr Cys Gly Arg Pro Ala Thr
50 55 60

Arg Ala Cys Asp Ala Ser Asp Pro Arg Arg Ala His Ser Pro Ala Leu
65 70 75 80

Leu Thr Ser Pro Gly Gly Thr Ala Ser Pro Leu Cys Trp Arg Ser Glu
85 90 95

Ser Leu Pro Arg Ala Pro Leu Asn Val Thr Leu Thr Val Pro Leu Gly
100 105 110

Lys Ala Phe Glu Leu Val Phe Val Ser Leu Arg Phe Cys Ser Ala Pro
115 120 125

Pro Ala Ser Val Ala Leu Leu Lys Ser Gln Asp His Gly Arg Ser Trp
130 135 140

Ala Pro Leu Gly Phe Phe Ser Ser His Cys Asp Leu Asp Tyr Gly Arg
145 150 155 160

Leu Pro Ala Pro Ala Asn Gly Pro Ala Gly Pro Gly Pro Glu Ala Leu
165 170 175

Cys Phe Pro Ala Pro Leu Ala Gln Pro Asp Gly Ser Gly Leu Leu Ala
180 185 190

Phe Ser Met Gln Asp Ser Ser Pro Pro Gly Leu Asp Leu Asp Ser Ser
195 200 205

Pro Val Leu Gln Asp Trp Val Thr Ala Thr Asp Val Arg Val Val Leu
210 215 220

Thr Arg Pro Ser Thr Ala Gly Asp Pro Arg Asp Met Glu Ala Val Val
225 230 235 240

Pro Tyr Ser Tyr Ala Ala Thr Asp Leu Gln Val Gly Gly Arg Cys Lys
245 250 255

Cys Asn Gly His Ala Ser Arg Cys Leu Leu Asp Thr Gln Gly His Leu
260 265 270

Ile Cys Asp Cys Arg His Gly Thr Glu Gly Pro Asp Cys Gly Arg Cys
275 280 285

Lys Pro Phe Tyr Cys Asp Arg Pro Trp Gln Arg Ala Thr Ala Arg Glu
290 295 300

Ser His Ala Cys Leu Ala Cys Ser Cys Asn Gly His Ala Arg Arg Cys
305 310 315 320

Arg Phe Asn Met Glu Leu Tyr Arg Leu Ser Gly Arg Arg Ser Gly Gly
325 330 335

Val Cys Leu Asn Cys Arg His Asn Thr Ala Gly Arg His Cys His Tyr
340 345 350

Cys Arg Glu Gly Phe Tyr Arg Asp Pro Gly Arg Ala Leu Ser Asp Arg
355 360 365

Arg Ala Cys Arg Ala Cys Asp Cys His Pro Val Gly Ala Ala Gly Lys
370 375 380

BNSDOCID: <WO___9748797A1_I_>

```
Thr Cys Asn Gln Thr Thr Gly Gln Cys Pro Cys Lys Asp Gly Val Thr
385                 390                 395                 400

Gly Leu Thr Cys Asn Arg Cys Ala Pro Gly Phe Gln Gln Ser Arg Ser
                405                 410                 415

Pro Val Ala Pro Cys Val Lys Thr Pro Ile Pro Gly Pro Thr Glu Asp
            420                 425                 430

Ser Ser Pro Val Gln Pro Gln Asp Cys Asp Ser His Cys Lys Pro Ala
        435                 440                 445

Arg Gly Ser Tyr Arg Ile Ser Leu Lys Lys Phe Cys Lys Lys Asp Tyr
    450                 455                 460

Ala Val Gln Val Ala Val Gly Ala Arg Gly Glu Ala Arg Gly Ala Trp
465                 470                 475                 480

Thr Arg Phe Pro Val Ala Val Leu Ala Val Phe Arg Ser Gly Glu Glu
                485                 490                 495

Arg Ala Arg Arg Gly Ser Ser Ala Leu Trp Val Pro Ala Gly Asp Ala
            500                 505                 510

Ala Cys Gly Cys Pro Arg Leu Leu Pro Gly Arg Arg Tyr Leu Leu Leu
        515                 520                 525

Gly Gly Gly Pro Gly Ala Ala Ala Gly Gly Ala Gly Gly Arg Gly Pro
    530                 535                 540

Gly Leu Ile Ala Ala Arg Gly Ser Leu Val Leu Pro Trp Arg Asp Ala
545                 550                 555                 560

Trp Thr Arg Arg Leu Arg Arg Leu Gln Arg Arg Glu Arg Arg Gly Arg
                565                 570                 575

Cys Ser Ala Ala
            580
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 606 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Met Pro Arg Arg Gly Ala Glu Gly Pro Leu Ala Leu Leu Leu Ala Ala
1               5                   10                  15

Ala Trp Leu Ala Gln Pro Leu Arg Gly Gly Tyr Pro Gly Leu Asn Met
            20                  25                  30

Phe Ala Val Gln Thr Ala Gln Pro Asp Pro Cys Tyr Asp Glu His Gly
        35                  40                  45

Leu Pro Arg Arg Cys Ile Pro Asp Phe Val Asn Ser Ala Phe Gly Lys
    50                  55                  60
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BNSDOCID: <WO___9748797A1_I_>

Glu Val Lys Val Ser Ser Thr Cys Gly Lys Pro Pro Ser Arg Tyr Cys
65 70 75 80

Val Val Thr Glu Lys Gly Glu Glu Gln Val Arg Ser Cys His Leu Cys
85 90 95

Asn Ala Ser Asp Pro Lys Arg Ala His Pro Pro Ser Phe Leu Thr Asp
100 105 110

Leu Asn Asn Pro His Asn Leu Thr Cys Trp Gln Ser Asp Ser Tyr Val
115 120 125

Gln Tyr Pro His Asn Val Thr Leu Thr Leu Ser Leu Gly Lys Lys Phe
130 135 140

Glu Val Thr Tyr Val Ser Leu Gln Phe Cys Ser Pro Arg Pro Glu Ser
145 150 155 160

Met Ala Ile Tyr Lys Ser Met Asp Tyr Gly Lys Thr Trp Val Pro Phe
165 170 175

Gln Phe Tyr Ser Thr Gln Cys Arg Lys Met Tyr Asn Lys Pro Ser Arg
180 185 190

Ala Ala Ile Thr Lys Gln Asn Glu Gln Gln Ala Ile Cys Thr Asp Ser
195 200 205

His Thr Asp Val Arg Pro Leu Ser Gly Gly Leu Ile Ala Phe Ser Thr
210 215 220

Leu Asp Gly Arg Pro Thr Ala His Asp Phe Asp Asn Ser Pro Val Leu
225 230 235 240

Gln Asp Trp Val Thr Ala Thr Asp Ile Lys Val Thr Phe Ser Arg Leu
245 250 255

His Thr Phe Gly Asp Glu Asn Glu Asp Asp Ser Glu Leu Ala Arg Asp
260 265 270

Ser Tyr Phe Tyr Ala Val Ser Asp Leu Gln Val Gly Gly Arg Cys Lys
275 280 285

Cys Asn Gly His Ala Ser Arg Cys Val Arg Asp Arg Asp Asp Asn Leu
290 295 300

Val Cys Asp Cys Lys His Asn Thr Ala Gly Pro Glu Cys Asp Arg Cys
305 310 315 320

Lys Pro Phe His Tyr Asp Arg Pro Trp Gln Arg Ala Thr Ala Arg Glu
325 330 335

Ala Asn Glu Cys Val Ala Cys Asn Cys Asn Leu His Ala Arg Arg Cys
340 345 350

Arg Phe Asn Met Glu Leu Tyr Lys Leu Ser Gly Arg Lys Ser Gly Gly
355 360 365

Val Cys Leu Asn Cys Arg His Asn Thr Ala Gly Arg His Cys His Tyr
370 375 380

Cys Lys Glu Gly Phe Tyr Arg Asp Leu Ser Lys Pro Ile Ser His Arg
385 390 395 400

Lys Ala Cys Lys Glu Cys Asp Cys His Pro Val Gly Ala Ala Gly Gln
405 410 415

BNSDOCID: <WO___9748797A1_I_>

Thr Cys Asn Gln Thr Thr Gly Gln Cys Pro Cys Lys Asp Gly Val Thr
420 425 430

Gly Ile Thr Cys Asn Arg Cys Ala Lys Gly Tyr Gln Gln Ser Arg Ser
435 440 445

Pro Ile Ala Pro Cys Ile Lys Ile Pro Ala Ala Pro Pro Pro Thr Ala
450 455 460

Ala Ser Ser Thr Glu Glu Pro Ala Asp Cys Asp Ser Tyr Cys Lys Ala
465 470 475 480

Ser Lys Gly Lys Leu Lys Ile Asn Met Lys Lys Tyr Cys Lys Lys Asp
485 490 495

Tyr Ala Val Gln Ile His Ile Leu Lys Ala Glu Lys Asn Ala Asp Trp
500 505 510

Trp Lys Phe Thr Val Asn Ile Ile Ser Val Tyr Lys Gln Gly Ser Asn
515 520 525

Arg Leu Arg Arg Gly Asp Gln Thr Leu Trp Val His Ala Lys Asp Ile
530 535 540

Ala Cys Lys Cys Pro Lys Val Lys Pro Met Lys Lys Tyr Leu Leu Leu
545 550 555 560

Gly Ser Thr Glu Asp Ser Pro Asp Gln Ser Gly Ile Ile Ala Asp Lys
565 570 575

Ser Ser Leu Val Ile Gln Trp Arg Asp Thr Trp Ala Arg Arg Leu Arg
580 585 590

Lys Phe Gln Gln Arg Glu Lys Lys Gly Lys Cys Arg Lys Ala
595 600 605

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 581 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Leu Arg Leu Leu Leu Thr Thr Ser Val Leu Arg Leu Ala Arg Ala Ala
1 5 10 15

Asn Pro Glu Val Ala Gln Gln Thr Pro Pro Asp Pro Cys Tyr Asp Glu
20 25 30

Ser Gly Ala Pro Arg Arg Cys Ile Pro Glu Phe Val Asn Ala Ala Phe
35 40 45

Gly Lys Glu Val Gln Ala Ser Ser Thr Cys Gly Lys Pro Pro Thr Arg
50 55 60

His Cys Asp Ala Ser Asp Pro Arg Arg Ala His Pro Pro Ala Tyr Leu
65 70 75 80

BNSDOCID: <WO___9748797A1_I_>

Thr Asp Leu Asn Thr Ala Ala Asn Met Thr Cys Trp Arg Ser Glu Thr
85 90 95

Leu His His Leu Pro His Asn Val Thr Leu Thr Leu Ser Leu Gly Lys
100 105 110

Lys Phe Glu Val Val Tyr Val Ser Leu Gln Phe Cys Ser Pro Arg Pro
115 120 125

Glu Ser Thr Ala Ile Phe Lys Ser Met Asp Tyr Gly Lys Thr Trp Val
130 135 140

Pro Tyr Gln Tyr Tyr Ser Ser Gln Cys Arg Lys Ile Tyr Gly Lys Pro
145 150 155 160

Ser Lys Ala Thr Val Thr Lys Gln Asn Glu Gln Glu Ala Leu Cys Thr
165 170 175

Asp Gly Leu Thr Asp Leu Tyr Pro Leu Thr Gly Gly Leu Ile Ala Phe
180 185 190

Ser Thr Leu Asp Gly Arg Pro Ser Ala Gln Asp Phe Asp Ser Ser Pro
195 200 205

Val Leu Gln Asp Trp Val Thr Ala Thr Asp Ile Arg Val Val Phe Ser
210 215 220

Arg Pro His Leu Phe Arg Glu Leu Gly Gly Arg Glu Ala Gly Glu Glu
225 230 235 240

Asp Gly Gly Ala Gly Ala Thr Pro Tyr Tyr Tyr Ser Val Gly Glu Leu
245 250 255

Gln Val Gly Gly Arg Cys Lys Cys Asn Gly His Ala Ser Arg Cys Val
260 265 270

Lys Asp Lys Glu Gln Lys Leu Val Cys Asp Cys Lys His Asn Thr Glu
275 280 285

Gly Pro Glu Cys Asp Arg Cys Lys Pro Phe His Tyr Asp Arg Pro Trp
290 295 300

Gln Arg Ala Ser Ala Arg Glu Ala Asn Glu Cys Leu Ala Cys Asn Cys
305 310 315 320

Asn Leu His Ala Arg Arg Cys Arg Phe Asn Met Glu Leu Tyr Lys Leu
325 330 335

Ser Gly Arg Lys Ser Gly Gly Val Cys Leu Asn Cys Arg His Asn Thr
340 345 350

Ala Gly Arg His Cys His Tyr Cys Lys Glu Gly Phe Tyr Arg Asp Leu
355 360 365

Ser Lys Ser Ile Thr Asp Arg Lys Ala Cys Lys Ala Cys Asp Cys His
370 375 380

Pro Val Gly Ala Ala Gly Lys Thr Cys Asn Gln Thr Thr Gly Gln Cys
385 390 395 400

Pro Cys Lys Asp Gly Val Thr Gly Leu Thr Cys Asn Arg Cys Ala Lys
405 410 415

Gly Phe Gln Gln Ser Arg Ser Pro Val Ala Pro Cys Ile Lys Ile Pro
420 425 430

BNSDOCID: <WO___9748797A1_I_>

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Ala Ile Asn Pro Thr Ser Leu Val Thr Ser Thr Glu Ala Pro Ala Asp
        435                 440                 445

Cys Asp Ser Tyr Cys Lys Pro Ala Lys Gly Asn Tyr Lys Ile Asn Met
    450                 455                 460

Lys Lys Tyr Cys Lys Lys Asp Tyr Val Val Gln Val Asn Ile Leu Glu
465                 470                 475                 480

Met Glu Thr Val Ala Asn Trp Ala Lys Phe Thr Ile Asn Ile Leu Ser
                485                 490                 495

Val Tyr Lys Cys Arg Asp Glu Arg Val Lys Arg Gly Asp Asn Phe Leu
            500                 505                 510

Trp Ile His Leu Lys Asp Leu Ser Cys Lys Cys Pro Lys Ile Gln Ile
        515                 520                 525

Ser Lys Lys Tyr Leu Val Met Gly Ile Ser Glu Asn Ser Thr Asp Arg
    530                 535                 540

Pro Gly Leu Met Ala Asp Lys Asn Ser Leu Val Ile Gln Trp Arg Asp
545                 550                 555                 560

Ala Trp Thr Arg Arg Leu Arg Lys Leu Gln Arg Arg Glu Lys Lys Gly
                565                 570                 575

Lys Cys Val Lys Pro
            580
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(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5894 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..5053

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

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G AAG GTC CTG GTG ACG GTC CTG GAA CTC TTC CTG CCA TTG CTG TTT          46
  Lys Val Leu Val Thr Val Leu Glu Leu Phe Leu Pro Leu Leu Phe
    1               5                  10                  15

TCT GGG ATC CTC ATC TGG CTC CGC TTG AAG ATT CAG TCG GAA AAT GTG        94
Ser Gly Ile Leu Ile Trp Leu Arg Leu Lys Ile Gln Ser Glu Asn Val
            20                  25                  30

CCC AAC GCC ACC ATC TAC CCG GGC CAG TCC ATC CAG GAG CTG CCT CTG       142
Pro Asn Ala Thr Ile Tyr Pro Gly Gln Ser Ile Gln Glu Leu Pro Leu
        35                  40                  45

TTC TTC ACC TTC CCT CCG CCA GGA GAC ACC TGG GAG CTT GCC TAC ATC       190
Phe Phe Thr Phe Pro Pro Pro Gly Asp Thr Trp Glu Leu Ala Tyr Ile
    50                  55                  60
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BNSDOCID: <WO___9748797A1_I_>

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CCT TCT CAC AGT GAC GCT GCC AAG GCC GTC ACT GAG ACA GTG CGC AGG      238
Pro Ser His Ser Asp Ala Ala Lys Ala Val Thr Glu Thr Val Arg Arg
      65                  70                  75

GCA CTT GTG ATC AAC ATG CGA GTG CGC GGC TTT CCC TCC GAG AAG GAC      286
Ala Leu Val Ile Asn Met Arg Val Arg Gly Phe Pro Ser Glu Lys Asp
 80                  85                  90                  95

TTT GAG GAC TAC ATT AGG TAC GAC AAC TGC TCG TCC AGC GTG CTG GCC      334
Phe Glu Asp Tyr Ile Arg Tyr Asp Asn Cys Ser Ser Ser Val Leu Ala
                100                 105                 110

GCC GTG GTC TTC GAG CAC CCC TTC AAC CAC AGC AAG GAG CCC CTG CCG      382
Ala Val Val Phe Glu His Pro Phe Asn His Ser Lys Glu Pro Leu Pro
            115                 120                 125

CTG GCG GTG AAA TAT CAC CTA CGG TTC AGT TAC ACA CGG AGA AAT TAC      430
Leu Ala Val Lys Tyr His Leu Arg Phe Ser Tyr Thr Arg Arg Asn Tyr
        130                 135                 140

ATG TGG ACC CAA ACA GGC TCC TTT TTC CTG AAA GAG ACA GAA GGC TGG      478
Met Trp Thr Gln Thr Gly Ser Phe Phe Leu Lys Glu Thr Glu Gly Trp
    145                 150                 155

CAC ACT ACT TCC CTT TTC CCG CTT TTC CCA AAC CCA GGA CCA AGG GAA      526
His Thr Thr Ser Leu Phe Pro Leu Phe Pro Asn Pro Gly Pro Arg Glu
160                 165                 170                 175

CTA ACA TCC CCT GAT GGC GGA GAA CCT GGG TAC ATC CGG GAA GGC TTC      574
Leu Thr Ser Pro Asp Gly Gly Glu Pro Gly Tyr Ile Arg Glu Gly Phe
                180                 185                 190

CTG GCC GTG CAG CAT GCT GTG GAC CGG GCC ATC ATG GAG TAC CAT GCC      622
Leu Ala Val Gln His Ala Val Asp Arg Ala Ile Met Glu Tyr His Ala
            195                 200                 205

GAT GCC GCC ACA CGC CAG CTG TTC CAG AGA CTG ACG GTG ACC ATC AAG      670
Asp Ala Ala Thr Arg Gln Leu Phe Gln Arg Leu Thr Val Thr Ile Lys
        210                 215                 220

AGG TTC CCG TAC CCG CCG TTC ATC GCA GAC CCC TTC CTC GTG GCC ATC      718
Arg Phe Pro Tyr Pro Pro Phe Ile Ala Asp Pro Phe Leu Val Ala Ile
    225                 230                 235

CAG TAC CAG CTG CCC CTG CTG CTG CTG CTC AGC TTC ACC TAC ACC GCG      766
Gln Tyr Gln Leu Pro Leu Leu Leu Leu Leu Ser Phe Thr Tyr Thr Ala
240                 245                 250                 255

CTC ACC ATT GCC CGT GCT GTC GTG CAG GAG AAG GAA AGG AGG CTG AAG      814
Leu Thr Ile Ala Arg Ala Val Val Gln Glu Lys Glu Arg Arg Leu Lys
                260                 265                 270

GAG TAC ATG CGC ATG ATG GGG CTC AGC AGC TGG CTG CAC TGG AGT GCC      862
Glu Tyr Met Arg Met Met Gly Leu Ser Ser Trp Leu His Trp Ser Ala
            275                 280                 285

TGG TTC CTC TTG TTC TTC TTC CTC TTC CTC CTC ATC GCC GCC TCC TTC ATG  910
Trp Phe Leu Leu Phe Phe Phe Leu Phe Leu Leu Ile Ala Ala Ser Phe Met
        290                 295                 300

ACC CTG CTC TTC TGT GTC AAG GTG AAG CCA AAT GTA GCC GTG CTG TCC      958
Thr Leu Leu Phe Cys Val Lys Val Lys Pro Asn Val Ala Val Leu Ser
    305                 310                 315
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CGC AGC GAC CCC TCC CTG GTG CTC GCC TTC CTG CTG TGC TTC GCC ATC      1006
Arg Ser Asp Pro Ser Leu Val Leu Ala Phe Leu Leu Cys Phe Ala Ile
320                 325                 330                 335

TCT ACC ATC TCC TTC AGC TTC ATG GTC AGC ACC TTC TTC AGC AAA GCC      1054
Ser Thr Ile Ser Phe Ser Phe Met Val Ser Thr Phe Phe Ser Lys Ala
                340                 345                 350

AAC ATG GCA GCA GCC TTC GGA GGC TTC CTC TAC TTC TTC ACC TAC ATC      1102
Asn Met Ala Ala Ala Phe Gly Gly Phe Leu Tyr Phe Phe Thr Tyr Ile
            355                 360                 365

CCC TAC TTC TTC GTG GCC CCT CGG TAC AAC TGG ATG ACT CTG AGC CAG      1150
Pro Tyr Phe Phe Val Ala Pro Arg Tyr Asn Trp Met Thr Leu Ser Gln
        370                 375                 380

AAG CTC TGC TCC TGC CTC CTG TCT AAT GTC GCC ATG GCA ATG GGA GCC      1198
Lys Leu Cys Ser Cys Leu Leu Ser Asn Val Ala Met Ala Met Gly Ala
    385                 390                 395

CAG CTC ATT GGG AAA TTT GAG GCG AAA GGC ATG GGC ATC CAG TGG CGA      1246
Gln Leu Ile Gly Lys Phe Glu Ala Lys Gly Met Gly Ile Gln Trp Arg
400                 405                 410                 415

GAC CTC CTG AGT CCC GTC AAC GTG GAC GAC GAC TTC TGC TTC GGG CAG      1294
Asp Leu Leu Ser Pro Val Asn Val Asp Asp Asp Phe Cys Phe Gly Gln
                420                 425                 430

GTG CTG GGG ATG CTG CTG CTG GAC TCT GTG CTC TAT GGC CTG GTG ACC      1342
Val Leu Gly Met Leu Leu Leu Asp Ser Val Leu Tyr Gly Leu Val Thr
            435                 440                 445

TGG TAC ATG GAG GCC GTC TTC CCA GGG CAG TTC GGC GTG CCT CAG CCC      1390
Trp Tyr Met Glu Ala Val Phe Pro Gly Gln Phe Gly Val Pro Gln Pro
        450                 455                 460

TGG TAC TTC TTC ATC ATG CCC TCC TAT TGG TGT GGG AAG CCA AGG GCG      1438
Trp Tyr Phe Phe Ile Met Pro Ser Tyr Trp Cys Gly Lys Pro Arg Ala
    465                 470                 475

GTT GCA GGG AAG GAG GAA GAA GAC AGT GAC CCC GAG AAA GCA CTC AGA      1486
Val Ala Gly Lys Glu Glu Glu Asp Ser Asp Pro Glu Lys Ala Leu Arg
480                 485                 490                 495

AAC GAG TAC TTT GAA GCC GAG CCA GAG GAC CTG GTG GCG GGG ATC AAG      1534
Asn Glu Tyr Phe Glu Ala Glu Pro Glu Asp Leu Val Ala Gly Ile Lys
                500                 505                 510

ATC AAG CAC CTG TCC AAG GTG TTC AGG GTG GGA AAT AAG GAC AGG GCG      1582
Ile Lys His Leu Ser Lys Val Phe Arg Val Gly Asn Lys Asp Arg Ala
            515                 520                 525

GCC GTC AGA GAC CTG AAC CTC AAC CTG TAC GAG GGA CAG ATC ACC GTC      1630
Ala Val Arg Asp Leu Asn Leu Asn Leu Tyr Glu Gly Gln Ile Thr Val
        530                 535                 540

CTG CTG GGC CAC AAC GGT GCC GGG AAG ACC ACC ACC CTC TCC ATG CTC      1678
Leu Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Met Leu
    545                 550                 555

ACA GGT CTC TTT CCC CCC ACC AGT GGA CGG GCA TAC ATC AGC GGG TAT      1726
Thr Gly Leu Phe Pro Pro Thr Ser Gly Arg Ala Tyr Ile Ser Gly Tyr
560                 565                 570                 575
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BNSDOCID: <WO___9748797A1_I_>

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GAA ATT TCC CAG GAC ATG GTT CAG ATC CGG AAG AGC CTG GGC CTG TGC      1774
Glu Ile Ser Gln Asp Met Val Gln Ile Arg Lys Ser Leu Gly Leu Cys
                580                 585                 590

CCG CAG CAC GAC ATC CTG TTT GAC AAC TTG ACA GTC GCA GAG CAC CTT      1822
Pro Gln His Asp Ile Leu Phe Asp Asn Leu Thr Val Ala Glu His Leu
            595                 600                 605

TAT TTC TAC GCC CAG CTG AAG GGC CTG TCA CGT CAG AAG TGC CCT GAA      1870
Tyr Phe Tyr Ala Gln Leu Lys Gly Leu Ser Arg Gln Lys Cys Pro Glu
        610                 615                 620

GAA GTC AAG CAG ATG CTG CAC ATC ATC GGC CTG GAG GAC AAG TGG AAC      1918
Glu Val Lys Gln Met Leu His Ile Ile Gly Leu Glu Asp Lys Trp Asn
    625                 630                 635

TCA CGG AGC CGC TTC CTG AGC GGG GGC ATG AGG CGC AAG CTC TCC ATC      1966
Ser Arg Ser Arg Phe Leu Ser Gly Gly Met Arg Arg Lys Leu Ser Ile
640                 645                 650                 655

GGC ATC GCC CTC ATC GCA GGC TCC AAG GTG CTG ATA CTG GAC GAG CCC      2014
Gly Ile Ala Leu Ile Ala Gly Ser Lys Val Leu Ile Leu Asp Glu Pro
                660                 665                 670

ACC TCG GGC ATG GAC GCC ATC TCC AGG AGG GCC ATC TGG GAT CTT CTT      2062
Thr Ser Gly Met Asp Ala Ile Ser Arg Arg Ala Ile Trp Asp Leu Leu
            675                 680                 685

CAG CGG CAG AAA AGT GAC CGC ACC ATC GTG CTG ACC ACC CAC TTC ATG      2110
Gln Arg Gln Lys Ser Asp Arg Thr Ile Val Leu Thr Thr His Phe Met
        690                 695                 700

GAC GAG GCT GAC CTG CTG GGA GAC CGC ATC GCC ATC ATG GCC AAG GGG      2158
Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Met Ala Lys Gly
    705                 710                 715

GAG CTG CAG TGC TGC GGG TCC TCG CTG TTC CTC AAG CAG AAA TAC GGT      2206
Glu Leu Gln Cys Cys Gly Ser Ser Leu Phe Leu Lys Gln Lys Tyr Gly
720                 725                 730                 735

GCC GGC TAT CAC ATG ACG CTG GTG AAG GAG CCG CAC TGC AAC CCG GAA      2254
Ala Gly Tyr His Met Thr Leu Val Lys Glu Pro His Cys Asn Pro Glu
                740                 745                 750

GAC ATC TCC CAG CTG GTC CAC CAC CAC GTG CCC AAC GCC ACG CTG GAG      2302
Asp Ile Ser Gln Leu Val His His His Val Pro Asn Ala Thr Leu Glu
            755                 760                 765

AGC AGC GCT GGG GCC GAG CTG TCT TTC ATC CTT CCC AGA GAG AGC ACG      2350
Ser Ser Ala Gly Ala Glu Leu Ser Phe Ile Leu Pro Arg Glu Ser Thr
        770                 775                 780

CAC AGG TTT GAA GGT CTC TTT GCT AAA CTG GAG AAG AAG CAG AAA GAG      2398
His Arg Phe Glu Gly Leu Phe Ala Lys Leu Glu Lys Lys Gln Lys Glu
    785                 790                 795

CTG GGC ATT GCC AGC TTT GGG GCA TCC ATC ACC ACC ATG GAG GAA GTC      2446
Leu Gly Ile Ala Ser Phe Gly Ala Ser Ile Thr Thr Met Glu Glu Val
800                 805                 810                 815

TTC CTT CGG GTC GGG AAG CTG GTG GAC AGC AGT ATG GAC ATC CAG GCC      2494
Phe Leu Arg Val Gly Lys Leu Val Asp Ser Ser Met Asp Ile Gln Ala
                820                 825                 830
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ATC CAG CTC CCT GCC CTG CAG TAC CAG CAC GAG AGG CGC GCC AGC GAC      2542
Ile Gln Leu Pro Ala Leu Gln Tyr Gln His Glu Arg Arg Ala Ser Asp
            835                 840                 845

TGG GCT GTG GAC AGC AAC CTC TGT GGG GCC ATG GAC CCC TCC GAC GGC      2590
Trp Ala Val Asp Ser Asn Leu Cys Gly Ala Met Asp Pro Ser Asp Gly
        850                 855                 860

ATT GGA GCC CTC ATC GAG GAG GAG CGC ACC GCT GTC AAG CTC AAC ACT      2638
Ile Gly Ala Leu Ile Glu Glu Glu Arg Thr Ala Val Lys Leu Asn Thr
    865                 870                 875

GGG CTC GCC CTG CAC TGC CAG CAA TTC TGG GCC ATG TTC CTG AAG AAG      2686
Gly Leu Ala Leu His Cys Gln Gln Phe Trp Ala Met Phe Leu Lys Lys
880                 885                 890                 895

GCC GCA TAC AGC TGG CGC GAG TGG AAA ATG GTG GCG GCA CAG GTC CTG      2734
Ala Ala Tyr Ser Trp Arg Glu Trp Lys Met Val Ala Ala Gln Val Leu
                900                 905                 910

GTG CCT CTG ACC TGC GTC ACC CTG GCC CTC CTG GCC ATC AAC TAC TCC      2782
Val Pro Leu Thr Cys Val Thr Leu Ala Leu Leu Ala Ile Asn Tyr Ser
            915                 920                 925

TCG GAG CTC TTC GAC GAC CCC ATG CTG AGG CTG ACC TTG GGC GAG TAC      2830
Ser Glu Leu Phe Asp Asp Pro Met Leu Arg Leu Thr Leu Gly Glu Tyr
        930                 935                 940

GGC AGA ACC GTC GTG CCC TTC TCA GTT CCC GGG ACC TCC CAG CTG GGT      2878
Gly Arg Thr Val Val Pro Phe Ser Val Pro Gly Thr Ser Gln Leu Gly
    945                 950                 955

CAG CAG CTG TCA GAG CAT CTG AAA GAC GCA CTG CAG GCT GAG GGA CAG      2926
Gln Gln Leu Ser Glu His Leu Lys Asp Ala Leu Gln Ala Glu Gly Gln
960                 965                 970                 975

GAG CCC CGC GAG GTG CTC GGT GAC CTG GAG GAG TTC TTG ATC TTC AGG      2974
Glu Pro Arg Glu Val Leu Gly Asp Leu Glu Glu Phe Leu Ile Phe Arg
                980                 985                 990

GCT TCT GTG GAG GGG GGC GGC TTT AAT GAG CGG TGC CTT GTG GCA GCG      3022
Ala Ser Val Glu Gly Gly Gly Phe Asn Glu Arg Cys Leu Val Ala Ala
            995                 1000                1005

TCC TTC AGA GAT GTG GGA GAG CGC ACG GTC GTC AAC GCC TTG TTC AAC      3070
Ser Phe Arg Asp Val Gly Glu Arg Thr Val Val Asn Ala Leu Phe Asn
        1010                1015                1020

AAC CAG GCG TAC CAC TCT CCA GCC ACT GCC CTG GCC GTC GTG GAC AAC      3118
Asn Gln Ala Tyr His Ser Pro Ala Thr Ala Leu Ala Val Val Asp Asn
    1025                1030                1035

CTT CTG TTC AAG CTG CTG TGC GGG CCT CAC GCC TCC ATT GTG GTC TCC      3166
Leu Leu Phe Lys Leu Leu Cys Gly Pro His Ala Ser Ile Val Val Ser
1040                1045                1050                1055

AAC TTC CCC CAG CCC CGG AGC GCC CTG CAG GCT GCC AAG GAC CAG TTT      3214
Asn Phe Pro Gln Pro Arg Ser Ala Leu Gln Ala Ala Lys Asp Gln Phe
                1060                1065                1070

AAC GAG GGC CGG AAG GGA TTC GAC ATT GCC CTC AAC CTG CTC TTC GCC      3262
Asn Glu Gly Arg Lys Gly Phe Asp Ile Ala Leu Asn Leu Leu Phe Ala
            1075                1080                1085
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ATG GCA TTC TTG GCC AGC ACG TTC TCC ATC CTG GCG GTC AGC GAG AGG      3310
Met Ala Phe Leu Ala Ser Thr Phe Ser Ile Leu Ala Val Ser Glu Arg
        1090                1095                1100

GCC GTG CAG GCC AAG CAT GTG CAG TTT GTG AGT GGA GTC CAC GTG GCC      3358
Ala Val Gln Ala Lys His Val Gln Phe Val Ser Gly Val His Val Ala
    1105                1110                1115

AGT TTC TGG CTC TCT GCT CTG CTG TGG GAC CTC ATC TCC TTC CTC ATC      3406
Ser Phe Trp Leu Ser Ala Leu Leu Trp Asp Leu Ile Ser Phe Leu Ile
1120                1125                1130                1135

CCC AGT CTG CTG CTG CTG GTG GTG TTT AAG GCC TTC GAC GTG CGT GCC      3454
Pro Ser Leu Leu Leu Leu Val Val Phe Lys Ala Phe Asp Val Arg Ala
                1140                1145                1150

TTC ACG CGG GAC GGC CAC ATG GCT GAC ACC CTG CTG CTG CTC CTG CTC      3502
Phe Thr Arg Asp Gly His Met Ala Asp Thr Leu Leu Leu Leu Leu Leu
            1155                1160                1165

TAC GGC TGG GCC ATC ATC CCC CTC ATG TAC CTG ATG AAC TTC TTC TTC      3550
Tyr Gly Trp Ala Ile Ile Pro Leu Met Tyr Leu Met Asn Phe Phe Phe
        1170                1175                1180

TTG GGG GCG GCC ACT GCC TAC ACG AGG CTG ACC ATC TTC AAC ATC CTG      3598
Leu Gly Ala Ala Thr Ala Tyr Thr Arg Leu Thr Ile Phe Asn Ile Leu
    1185                1190                1195

TCA GGC ATC GCC ACC TTC CTG ATG GTC ACC ATC ATG CGC ATC CCA GCT      3646
Ser Gly Ile Ala Thr Phe Leu Met Val Thr Ile Met Arg Ile Pro Ala
1200                1205                1210                1215

GTA AAA CTG GAA GAA CTT TCC AAA ACC CTG GAT CAC GTG TTC CTG GTG      3694
Val Lys Leu Glu Glu Leu Ser Lys Thr Leu Asp His Val Phe Leu Val
                1220                1225                1230

CTG CCC AAC CAC TGT CTG GGG ATG GCA GTC AGC AGT TTC TAC GAG AAC      3742
Leu Pro Asn His Cys Leu Gly Met Ala Val Ser Ser Phe Tyr Glu Asn
            1235                1240                1245

TAC GAG ACG CGG AGG TAC TGC ACC TCC TCC GAG GTC GCC GCC CAC TAC      3790
Tyr Glu Thr Arg Arg Tyr Cys Thr Ser Ser Glu Val Ala Ala His Tyr
        1250                1255                1260

TGC AAG AAA TAT AAC ATC CAG TAC CAG GAG AAC TTC TAT GCC TGG AGC      3838
Cys Lys Lys Tyr Asn Ile Gln Tyr Gln Glu Asn Phe Tyr Ala Trp Ser
    1265                1270                1275

GCC CCG GGG GTC GGC CGG TTT GTG GCC TCC ATG GCC GCC TCA GGG TGC      3886
Ala Pro Gly Val Gly Arg Phe Val Ala Ser Met Ala Ala Ser Gly Cys
1280                1285                1290                1295

GCC TAC CTC ATC CTG CTC TTC CTC ATC GAG ACC AAC CTG CTT CAG AGA      3934
Ala Tyr Leu Ile Leu Leu Phe Leu Ile Glu Thr Asn Leu Leu Gln Arg
                1300                1305                1310

CTC AGG GGC ATC CTC TGC GCC CTC CGG AGG AGG CGG ACA CTG ACA GAA      3982
Leu Arg Gly Ile Leu Cys Ala Leu Arg Arg Arg Arg Thr Leu Thr Glu
            1315                1320                1325

TTA TAC ACC CGG ATG CCT GTG CTT CCT GAG GAC CAA GAT GTA GCG GAC      4030
Leu Tyr Thr Arg Met Pro Val Leu Pro Glu Asp Gln Asp Val Ala Asp
        1330                1335                1340
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BNSDOCID: <WO___9748797A1_I_>

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GAG AGG ACC CGC ATC CTG GCC CCC AGC CCG GAC TCC CTG CTC CAC ACA      4078
Glu Arg Thr Arg Ile Leu Ala Pro Ser Pro Asp Ser Leu Leu His Thr
     1345                1350                1355

CCT CTG ATT ATC AAG GAG CTC TCC AAG GTG TAC GAG CAG CGG GTG CCC      4126
Pro Leu Ile Ile Lys Glu Leu Ser Lys Val Tyr Glu Gln Arg Val Pro
1360                1365                1370                1375

CTC CTG GCC GTG GAC AGG CTC TCC CTC GCG GTG CAG AAA GGG GAG TGC      4174
Leu Leu Ala Val Asp Arg Leu Ser Leu Ala Val Gln Lys Gly Glu Cys
                1380                1385                1390

TTC GGC CTG CTG GGC TTC AAT GGA GCC GGG AAG ACC ACG ACT TTC AAA      4222
Phe Gly Leu Leu Gly Phe Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys
           1395                1400                1405

ATG CTG ACC GGG GAG GAG AGC CTC ACT TCT GGG GAT GCC TTT GTC GGG      4270
Met Leu Thr Gly Glu Glu Ser Leu Thr Ser Gly Asp Ala Phe Val Gly
      1410                1415                1420

GGT CAC AGA ATC AGC TCT GAT GTC GGA AAG GTG CGG CAG CGG ATC GGC      4318
Gly His Arg Ile Ser Ser Asp Val Gly Lys Val Arg Gln Arg Ile Gly
     1425                1430                1435

TAC TGC CCG CAG TTT GAT GCC TTG CTG GAC CAC ATG ACA GGC CGG GAG      4366
Tyr Cys Pro Gln Phe Asp Ala Leu Leu Asp His Met Thr Gly Arg Glu
1440                1445                1450                1455

ATG CTG GTC ATG TAC GCT CGG CTC CGG GGC ATC CCT GAG CGC CAC ATC      4414
Met Leu Val Met Tyr Ala Arg Leu Arg Gly Ile Pro Glu Arg His Ile
                1460                1465                1470

GGG GCC TGC GTG GAG AAC ACT CTG CGG GGC CTG CTG CTG GAG CCA CAT      4462
Gly Ala Cys Val Glu Asn Thr Leu Arg Gly Leu Leu Leu Glu Pro His
           1475                1480                1485

GCC AAC AAG CTG GTC AGG ACG TAC AGT GGT GGT AAC AAG CGG AAG CTG      4510
Ala Asn Lys Leu Val Arg Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu
      1490                1495                1500

AGC ACC GGC ATC GCC CTG ATC GGA GAG CCT GCT GTC ATC TTC CTG GAC      4558
Ser Thr Gly Ile Ala Leu Ile Gly Glu Pro Ala Val Ile Phe Leu Asp
     1505                1510                1515

GAG CCG TCC ACT GGC ATG GAC CCC GTG GCC CGG CGC CTG CTT TGG GAC      4606
Glu Pro Ser Thr Gly Met Asp Pro Val Ala Arg Arg Leu Leu Trp Asp
1520                1525                1530                1535

ACC GTG GCA CGA GCC CGA GAG TCT GGC AAG GCC ATC ATC ATC ACC TCC      4654
Thr Val Ala Arg Ala Arg Glu Ser Gly Lys Ala Ile Ile Ile Thr Ser
                1540                1545                1550

CAC AGC ATG GAG GAG TGT GAG GCC CTG TGC ACC CGG CTG GCC ATC ATG      4702
His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met
           1555                1560                1565

GTG CAG GGG CAG TTC AAG TGC CTG GGC AGC CCC CAG CAC CTC AAG AGC      4750
Val Gln Gly Gln Phe Lys Cys Leu Gly Ser Pro Gln His Leu Lys Ser
      1570                1575                1580

AAG TTC GGC AGC GGC TAC TCC CTG CGG GCC AAG GTG CAG AGT GAA GGG      4798
Lys Phe Gly Ser Gly Tyr Ser Leu Arg Ala Lys Val Gln Ser Glu Gly
     1585                1590                1595
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BNSDOCID: <WO___9748797A1_I_>

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CAA CAG GAG GCG CTG GAG GAG TTC AAG GCC TTC GTG GAC CTG ACC TTT      4846
Gln Gln Glu Ala Leu Glu Glu Phe Lys Ala Phe Val Asp Leu Thr Phe
1600                 1605                 1610                 1615

CCA GGC AGC GTC CTG GAA GAT GAG CAC CAA GGC ATG GTC CAT TAC CAC      4894
Pro Gly Ser Val Leu Glu Asp Glu His Gln Gly Met Val His Tyr His
                1620                 1625                 1630

CTG CCG GGC CGT GAC CTC AGC TGG GCG AAG GTT TTC GGT ATT CTG GAG      4942
Leu Pro Gly Arg Asp Leu Ser Trp Ala Lys Val Phe Gly Ile Leu Glu
            1635                 1640                 1645

AAA GCC AAG GAA AAG TAC GGC GTG GAC GAC TAC TCC GTG AGC CAG ATC      4990
Lys Ala Lys Glu Lys Tyr Gly Val Asp Asp Tyr Ser Val Ser Gln Ile
        1650                 1655                 1660

TCG CTG GAA CAG GTC TTC CTG AGC TTC GCC CAC CTG CAG CCG CCC ACC      5038
Ser Leu Glu Gln Val Phe Leu Ser Phe Ala His Leu Gln Pro Pro Thr
    1665                 1670                 1675

GCA GAG GAG GGG CGA TGAGGGGTGG CGGCTGTCTC GCCATCAGGC AGGGACAGGA      5093
Ala Glu Glu Gly Arg
1680

CGGGCAAGCA GGGCCCATCT TACATCCTCT CTCTCCAAGT TTATCTCATC CTTTATTTTT    5153

AATCACTTTT TTCTATGATG GATATGAAAA ATTCAAGGCA GTATGCACAG AATGGACGAG    5213

TGCAGCCCAG CCCTCATGCC CAGGATCAGC ATGCGCATCT CCATGTCTGC ATACTCTGGA    5273

GTTCACTTTC CCAGAGCTGG GGCAGGCCGG GCAGTCTGCG GGCAAGCTCC GGGGTCTCTG    5333

GGTGGAGAGC TGACCCAGGA AGGGCTGCAG CTGAGCTGGG GGTTGAATTT CTCCAGGCAC    5393

TCCCTGGAGA GAGGACCCAG TGACTTGTCC AAGTTTACAC ACGACACTAA TCTCCCCTGG    5453

GGAGGAAGCG GGAAGCCAGC CAGGTTGAAC TGTAGCGAGG CCCCCAGGCC GCCAGGAATG    5513

GACCATGCAG ATCACTGTCA GTGGAGGGAA GCTGCTGACT GTGATTAGGT GCTGGGGTCT    5573

TAGCGTCCAG CGCAGCCCGG GGGCATCCTG GAGGCTCTGC TCCTTAGGGC ATGGTAGTCA    5633

CCGCGAAGCC GGGCACCGTC CCACAGCATC TCCTAGAAGC AGCCGGCACA GGAGGGAAGG    5693

TGGCCAGGCT CGAAGCAGTC TCTGTTTCCA GCACTGCACC CTCAGGAAGT CGCCCGCCCC    5753

AGGACACGCA GGGACCACCC TAAGGGCTGG GTGGCTGTCT CAAGGACACA TTGAATACGT    5813

TGTGACCATC CAGAAAATAA ATGCTGAGGG GACACAAAAA AAAAAAAAAA AAAAAAAAAA    5873

AAAAAAAAAA AAAAAAAAAA A                                               5894
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1684 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

BNSDOCID: <WO___9748797A1_I_>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Lys Val Leu Val Thr Val Leu Glu Leu Phe Leu Pro Leu Leu Phe Ser
1 5 10 15

Gly Ile Leu Ile Trp Leu Arg Leu Lys Ile Gln Ser Glu Asn Val Pro
20 25 30

Asn Ala Thr Ile Tyr Pro Gly Gln Ser Ile Gln Glu Leu Pro Leu Phe
35 40 45

Phe Thr Phe Pro Pro Pro Gly Asp Thr Trp Glu Leu Ala Tyr Ile Pro
50 55 60

Ser His Ser Asp Ala Ala Lys Ala Val Thr Glu Thr Val Arg Arg Ala
65 70 75 80

Leu Val Ile Asn Met Arg Val Arg Gly Phe Pro Ser Glu Lys Asp Phe
85 90 95

Glu Asp Tyr Ile Arg Tyr Asp Asn Cys Ser Ser Ser Val Leu Ala Ala
100 105 110

Val Val Phe Glu His Pro Phe Asn His Ser Lys Glu Pro Leu Pro Leu
115 120 125

Ala Val Lys Tyr His Leu Arg Phe Ser Tyr Thr Arg Arg Asn Tyr Met
130 135 140

Trp Thr Gln Thr Gly Ser Phe Phe Leu Lys Glu Thr Glu Gly Trp His
145 150 155 160

Thr Thr Ser Leu Phe Pro Leu Phe Pro Asn Pro Gly Pro Arg Glu Leu
165 170 175

Thr Ser Pro Asp Gly Gly Glu Pro Gly Tyr Ile Arg Glu Gly Phe Leu
180 185 190

Ala Val Gln His Ala Val Asp Arg Ala Ile Met Glu Tyr His Ala Asp
195 200 205

Ala Ala Thr Arg Gln Leu Phe Gln Arg Leu Thr Val Thr Ile Lys Arg
210 215 220

Phe Pro Tyr Pro Pro Phe Ile Ala Asp Pro Phe Leu Val Ala Ile Gln
225 230 235 240

Tyr Gln Leu Pro Leu Leu Leu Leu Leu Ser Phe Thr Tyr Thr Ala Leu
245 250 255

Thr Ile Ala Arg Ala Val Val Gln Glu Lys Glu Arg Arg Leu Lys Glu
260 265 270

Tyr Met Arg Met Met Gly Leu Ser Ser Trp Leu His Trp Ser Ala Trp
275 280 285

Phe Leu Leu Phe Phe Leu Phe Leu Leu Ile Ala Ala Ser Phe Met Thr
290 295 300

Leu Leu Phe Cys Val Lys Val Lys Pro Asn Val Ala Val Leu Ser Arg
305 310 315 320

Ser Asp Pro Ser Leu Val Leu Ala Phe Leu Leu Cys Phe Ala Ile Ser
325 330 335

BNSDOCID: <WO___9748797A1_I_>

Thr Ile Ser Phe Ser Phe Met Val Ser Thr Phe Phe Ser Lys Ala Asn
340 345 350

Met Ala Ala Ala Phe Gly Gly Phe Leu Tyr Phe Phe Thr Tyr Ile Pro
355 360 365

Tyr Phe Phe Val Ala Pro Arg Tyr Asn Trp Met Thr Leu Ser Gln Lys
370 375 380

Leu Cys Ser Cys Leu Leu Ser Asn Val Ala Met Ala Met Gly Ala Gln
385 390 395 400

Leu Ile Gly Lys Phe Glu Ala Lys Gly Met Gly Ile Gln Trp Arg Asp
405 410 415

Leu Leu Ser Pro Val Asn Val Asp Asp Asp Phe Cys Phe Gly Gln Val
420 425 430

Leu Gly Met Leu Leu Leu Asp Ser Val Leu Tyr Gly Leu Val Thr Trp
435 440 445

Tyr Met Glu Ala Val Phe Pro Gly Gln Phe Gly Val Pro Gln Pro Trp
450 455 460

Tyr Phe Phe Ile Met Pro Ser Tyr Trp Cys Gly Lys Pro Arg Ala Val
465 470 475 480

Ala Gly Lys Glu Glu Glu Asp Ser Asp Pro Glu Lys Ala Leu Arg Asn
485 490 495

Glu Tyr Phe Glu Ala Glu Pro Glu Asp Leu Val Ala Gly Ile Lys Ile
500 505 510

Lys His Leu Ser Lys Val Phe Arg Val Gly Asn Lys Asp Arg Ala Ala
515 520 525

Val Arg Asp Leu Asn Leu Asn Leu Tyr Glu Gly Gln Ile Thr Val Leu
530 535 540

Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Met Leu Thr
545 550 555 560

Gly Leu Phe Pro Pro Thr Ser Gly Arg Ala Tyr Ile Ser Gly Tyr Glu
565 570 575

Ile Ser Gln Asp Met Val Gln Ile Arg Lys Ser Leu Gly Leu Cys Pro
580 585 590

Gln His Asp Ile Leu Phe Asp Asn Leu Thr Val Ala Glu His Leu Tyr
595 600 605

Phe Tyr Ala Gln Leu Lys Gly Leu Ser Arg Gln Lys Cys Pro Glu Glu
610 615 620

Val Lys Gln Met Leu His Ile Ile Gly Leu Glu Asp Lys Trp Asn Ser
625 630 635 640

Arg Ser Arg Phe Leu Ser Gly Gly Met Arg Arg Lys Leu Ser Ile Gly
645 650 655

Ile Ala Leu Ile Ala Gly Ser Lys Val Leu Ile Leu Asp Glu Pro Thr
660 665 670

Ser Gly Met Asp Ala Ile Ser Arg Arg Ala Ile Trp Asp Leu Leu Gln
675 680 685

BNSDOCID: <WO___9748797A1_I_>

Arg Gln Lys Ser Asp Arg Thr Ile Val Leu Thr Thr His Phe Met Asp
690 695 700

Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Met Ala Lys Gly Glu
705 710 715 720

Leu Gln Cys Cys Gly Ser Ser Leu Phe Leu Lys Gln Lys Tyr Gly Ala
725 730 735

Gly Tyr His Met Thr Leu Val Lys Glu Pro His Cys Asn Pro Glu Asp
740 745 750

Ile Ser Gln Leu Val His His His Val Pro Asn Ala Thr Leu Glu Ser
755 760 765

Ser Ala Gly Ala Glu Leu Ser Phe Ile Leu Pro Arg Glu Ser Thr His
770 775 780

Arg Phe Glu Gly Leu Phe Ala Lys Leu Glu Lys Lys Gln Lys Glu Leu
785 790 795 800

Gly Ile Ala Ser Phe Gly Ala Ser Ile Thr Thr Met Glu Glu Val Phe
805 810 815

Leu Arg Val Gly Lys Leu Val Asp Ser Ser Met Asp Ile Gln Ala Ile
820 825 830

Gln Leu Pro Ala Leu Gln Tyr Gln His Glu Arg Arg Ala Ser Asp Trp
835 840 845

Ala Val Asp Ser Asn Leu Cys Gly Ala Met Asp Pro Ser Asp Gly Ile
850 855 860

Gly Ala Leu Ile Glu Glu Glu Arg Thr Ala Val Lys Leu Asn Thr Gly
865 870 875 880

Leu Ala Leu His Cys Gln Gln Phe Trp Ala Met Phe Leu Lys Lys Ala
885 890 895

Ala Tyr Ser Trp Arg Glu Trp Lys Met Val Ala Ala Gln Val Leu Val
900 905 910

Pro Leu Thr Cys Val Thr Leu Ala Leu Leu Ala Ile Asn Tyr Ser Ser
915 920 925

Glu Leu Phe Asp Asp Pro Met Leu Arg Leu Thr Leu Gly Glu Tyr Gly
930 935 940

Arg Thr Val Val Pro Phe Ser Val Pro Gly Thr Ser Gln Leu Gly Gln
945 950 955 960

Gln Leu Ser Glu His Leu Lys Asp Ala Leu Gln Ala Glu Gly Gln Glu
965 970 975

Pro Arg Glu Val Leu Gly Asp Leu Glu Glu Phe Leu Ile Phe Arg Ala
980 985 990

Ser Val Glu Gly Gly Gly Phe Asn Glu Arg Cys Leu Val Ala Ala Ser
995 1000 1005

Phe Arg Asp Val Gly Glu Arg Thr Val Val Asn Ala Leu Phe Asn Asn
1010 1015 1020

Gln Ala Tyr His Ser Pro Ala Thr Ala Leu Ala Val Val Asp Asn Leu
1025 1030 1035 1040

BNSDOCID: <WO___9748797A1_I_>

Leu Phe Lys Leu Leu Cys Gly Pro His Ala Ser Ile Val Val Ser Asn
1045 1050 1055

Phe Pro Gln Pro Arg Ser Ala Leu Gln Ala Ala Lys Asp Gln Phe Asn
1060 1065 1070

Glu Gly Arg Lys Gly Phe Asp Ile Ala Leu Asn Leu Leu Phe Ala Met
1075 1080 1085

Ala Phe Leu Ala Ser Thr Phe Ser Ile Leu Ala Val Ser Glu Arg Ala
1090 1095 1100

Val Gln Ala Lys His Val Gln Phe Val Ser Gly Val His Val Ala Ser
1105 1110 1115 1120

Phe Trp Leu Ser Ala Leu Leu Trp Asp Leu Ile Ser Phe Leu Ile Pro
1125 1130 1135

Ser Leu Leu Leu Leu Val Val Phe Lys Ala Phe Asp Val Arg Ala Phe
1140 1145 1150

Thr Arg Asp Gly His Met Ala Asp Thr Leu Leu Leu Leu Leu Leu Tyr
1155 1160 1165

Gly Trp Ala Ile Ile Pro Leu Met Tyr Leu Met Asn Phe Phe Phe Leu
1170 1175 1180

Gly Ala Ala Thr Ala Tyr Thr Arg Leu Thr Ile Phe Asn Ile Leu Ser
1185 1190 1195 1200

Gly Ile Ala Thr Phe Leu Met Val Thr Ile Met Arg Ile Pro Ala Val
1205 1210 1215

Lys Leu Glu Glu Leu Ser Lys Thr Leu Asp His Val Phe Leu Val Leu
1220 1225 1230

Pro Asn His Cys Leu Gly Met Ala Val Ser Ser Phe Tyr Glu Asn Tyr
1235 1240 1245

Glu Thr Arg Arg Tyr Cys Thr Ser Ser Glu Val Ala Ala His Tyr Cys
1250 1255 1260

Lys Lys Tyr Asn Ile Gln Tyr Gln Glu Asn Phe Tyr Ala Trp Ser Ala
1265 1270 1275 1280

Pro Gly Val Gly Arg Phe Val Ala Ser Met Ala Ala Ser Gly Cys Ala
1285 1290 1295

Tyr Leu Ile Leu Leu Phe Leu Ile Glu Thr Asn Leu Leu Gln Arg Leu
1300 1305 1310

Arg Gly Ile Leu Cys Ala Leu Arg Arg Arg Arg Thr Leu Thr Glu Leu
1315 1320 1325

Tyr Thr Arg Met Pro Val Leu Pro Glu Asp Gln Asp Val Ala Asp Glu
1330 1335 1340

Arg Thr Arg Ile Leu Ala Pro Ser Pro Asp Ser Leu Leu His Thr Pro
1345 1350 1355 1360

Leu Ile Ile Lys Glu Leu Ser Lys Val Tyr Glu Gln Arg Val Pro Leu
1365 1370 1375

Leu Ala Val Asp Arg Leu Ser Leu Ala Val Gln Lys Gly Glu Cys Phe
1380 1385 1390

BNSDOCID: <WO___9748797A1_I_>

Gly Leu Leu Gly Phe Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys Met
1395 1400 1405

Leu Thr Gly Glu Glu Ser Leu Thr Ser Gly Asp Ala Phe Val Gly Gly
1410 1415 1420

His Arg Ile Ser Ser Asp Val Gly Lys Val Arg Gln Arg Ile Gly Tyr
1425 1430 1435 1440

Cys Pro Gln Phe Asp Ala Leu Leu Asp His Met Thr Gly Arg Glu Met
1445 1450 1455

Leu Val Met Tyr Ala Arg Leu Arg Gly Ile Pro Glu Arg His Ile Gly
1460 1465 1470

Ala Cys Val Glu Asn Thr Leu Arg Gly Leu Leu Leu Glu Pro His Ala
1475 1480 1485

Asn Lys Leu Val Arg Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser
1490 1495 1500

Thr Gly Ile Ala Leu Ile Gly Glu Pro Ala Val Ile Phe Leu Asp Glu
1505 1510 1515 1520

Pro Ser Thr Gly Met Asp Pro Val Ala Arg Arg Leu Leu Trp Asp Thr
1525 1530 1535

Val Ala Arg Ala Arg Glu Ser Gly Lys Ala Ile Ile Ile Thr Ser His
1540 1545 1550

Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val
1555 1560 1565

Gln Gly Gln Phe Lys Cys Leu Gly Ser Pro Gln His Leu Lys Ser Lys
1570 1575 1580

Phe Gly Ser Gly Tyr Ser Leu Arg Ala Lys Val Gln Ser Glu Gly Gln
1585 1590 1595 1600

Gln Glu Ala Leu Glu Glu Phe Lys Ala Phe Val Asp Leu Thr Phe Pro
1605 1610 1615

Gly Ser Val Leu Glu Asp Glu His Gln Gly Met Val His Tyr His Leu
1620 1625 1630

Pro Gly Arg Asp Leu Ser Trp Ala Lys Val Phe Gly Ile Leu Glu Lys
1635 1640 1645

Ala Lys Glu Lys Tyr Gly Val Asp Asp Tyr Ser Val Ser Gln Ile Ser
1650 1655 1660

Leu Glu Gln Val Phe Leu Ser Phe Ala His Leu Gln Pro Pro Thr Ala
1665 1670 1675 1680

Glu Glu Gly Arg

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1375 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

BNSDOCID: <WO___9748797A1_I_>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Cys Met Glu Glu Glu Pro Thr His Leu Arg Leu Gly Val Ser Ile Gln
1 5 10 15

Asn Leu Val Lys Val Tyr Arg Asp Gly Met Lys Val Ala Val Asp Gly
20 25 30

Leu Ala Leu Asn Phe Tyr Glu Gly Gln Ile Thr Ser Phe Leu Gly His
35 40 45

Asn Gly Ala Gly Lys Thr Thr Thr Met Ser Ile Leu Thr Gly Leu Phe
50 55 60

Pro Pro Thr Ser Gly Thr Ala Tyr Ile Leu Gly Lys Asp Ile Arg Ser
65 70 75 80

Glu Met Ser Ser Ile Arg Gln Asn Leu Gly Val Cys Pro Gln His Asn
85 90 95

Val Leu Phe Asp Met Leu Thr Val Glu Glu His Ile Trp Phe Tyr Ala
100 105 110

Arg Leu Lys Gly Leu Ser Glu Lys His Val Lys Ala Glu Met Glu Gln
115 120 125

Met Ala Leu Asp Val Gly Leu Pro Pro Ser Lys Leu Lys Ser Lys Thr
130 135 140

Ser Gln Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val Ala Leu Ala
145 150 155 160

Phe Val Gly Gly Ser Lys Val Val Ile Leu Asp Glu Pro Thr Ala Gly
165 170 175

Val Asp Pro Tyr Ser Arg Arg Gly Ile Trp Glu Leu Leu Leu Lys Tyr
180 185 190

Arg Gln Gly Arg Thr Ile Ile Leu Ser Thr His His Met Asp Glu Ala
195 200 205

Asp Ile Leu Gly Asp Arg Ile Ala Ile Ile Ser His Gly Lys Leu Cys
210 215 220

Cys Val Gly Ser Ser Leu Phe Leu Lys Asn Gln Leu Gly Thr Gly Tyr
225 230 235 240

Tyr Leu Thr Leu Val Lys Lys Asp Val Glu Ser Ser Leu Ser Ser Cys
245 250 255

Arg Asn Ser Ser Ser Thr Val Ser Cys Leu Lys Lys Glu Asp Ser Val
260 265 270

Ser Gln Ser Ser Ser Asp Ala Gly Leu Gly Ser Asp His Glu Ser Asp
275 280 285

Thr Leu Thr Ile Asp Val Ser Ala Ile Ser Asn Leu Ile Arg Lys His
290 295 300

Val Ser Glu Ala Arg Leu Val Glu Asp Ile Gly His Glu Leu Thr Tyr
305 310 315 320

BNSDOCID: <WO___9748797A1_I_>

Val Leu Pro Tyr Glu Ala Ala Lys Glu Gly Ala Phe Val Glu Leu Phe
325 330 335

His Glu Ile Asp Asp Arg Leu Ser Asp Leu Gly Ile Ser Ser Tyr Gly
340 345 350

Ile Ser Glu Thr Thr Leu Glu Glu Ile Phe Leu Lys Val Ala Glu Glu
355 360 365

Ser Gly Val Asp Ala Glu Thr Ser Asp Gly Thr Leu Pro Ala Arg Arg
370 375 380

Asn Arg Arg Ala Phe Gly Asp Lys Gln Ser Cys Leu His Pro Phe Thr
385 390 395 400

Glu Asp Asp Ala Val Asp Pro Asn Asp Ser Asp Ile Asp Pro Glu Ser
405 410 415

Arg Glu Thr Asp Leu Leu Ser Gly Met Asp Gly Lys Gly Ser Tyr Gln
420 425 430

Leu Lys Gly Trp Lys Leu Thr Gln Gln Gln Phe Val Ala Leu Leu Trp
435 440 445

Lys Arg Leu Leu Ile Ala Arg Arg Ser Arg Lys Gly Phe Phe Ala Gln
450 455 460

Ile Val Leu Pro Ala Val Phe Val Cys Ile Ala Leu Val Phe Ser Leu
465 470 475 480

Ile Val Pro Pro Phe Gly Lys Tyr Pro Ser Leu Glu Leu Gln Pro Trp
485 490 495

Met Tyr Asn Glu Gln Tyr Thr Phe Val Ser Asn Asp Ala Pro Glu Asp
500 505 510

Met Gly Thr Gln Glu Leu Leu Asn Ala Leu Thr Lys Asp Pro Gly Phe
515 520 525

Gly Thr Arg Cys Met Glu Gly Asn Pro Ile Pro Asp Thr Pro Cys Leu
530 535 540

Ala Gly Glu Glu Asp Trp Thr Ile Ser Pro Val Pro Gln Ser Ile Val
545 550 555 560

Asp Leu Phe Gln Asn Gly Asn Trp Thr Met Lys Asn Pro Ser Pro Ala
565 570 575

Cys Gln Cys Ser Ser Asp Lys Ile Lys Lys Met Leu Pro Val Cys Pro
580 585 590

Pro Gly Ala Gly Gly Leu Pro Pro Pro Gln Arg Lys Gln Lys Thr Ala
595 600 605

Asp Ile Leu Gln Asn Leu Thr Gly Arg Asn Ile Ser Asp Tyr Leu Val
610 615 620

Lys Thr Tyr Val Gln Ile Ile Ala Lys Ser Leu Lys Asn Lys Ile Trp
625 630 635 640

Val Asn Glu Phe Arg Tyr Gly Gly Phe Ser Leu Gly Val Ser Asn Ser
645 650 655

Gln Ala Leu Pro Pro Ser His Glu Val Asn Asp Ala Ile Lys Gln Met
660 665 670

BNSDOCID: <WO___9748797A1_I_>

Lys Lys Leu Leu Lys Leu Thr Lys Asp Thr Ser Ala Asp Arg Phe Leu
675 680 685

Ser Ser Leu Gly Arg Phe Met Ala Gly Leu Asp Thr Lys Asn Asn Val
690 695 700

Lys Val Trp Phe Asn Asn Lys Gly Trp His Ala Ile Ser Ser Phe Leu
705 710 715 720

Asn Val Ile Asn Asn Ala Ile Leu Arg Ala Asn Leu Gln Lys Gly Glu
725 730 735

Asn Pro Ser Gln Tyr Gly Ile Thr Ala Phe Asn His Pro Leu Asn Leu
740 745 750

Thr Lys Gln Gln Leu Ser Glu Val Ala Leu Met Thr Thr Ser Val Asp
755 760 765

Val Leu Val Ser Ile Cys Val Ile Phe Ala Met Ser Phe Val Pro Ala
770 775 780

Ser Phe Val Val Phe Leu Ile Gln Glu Arg Val Ser Lys Ala Lys His
785 790 795 800

Leu Gln Phe Ile Ser Gly Val Lys Pro Val Ile Tyr Trp Leu Ser Asn
805 810 815

Phe Val Trp Asp Met Cys Asn Tyr Val Val Pro Ala Thr Leu Val Ile
820 825 830

Ile Ile Phe Ile Cys Phe Gln Gln Lys Ser Tyr Val Ser Ser Thr Asn
835 840 845

Leu Pro Val Leu Ala Leu Leu Leu Leu Leu Tyr Gly Trp Ser Ile Thr
850 855 860

Pro Leu Met Tyr Pro Ala Ser Phe Val Phe Lys Ile Pro Ser Thr Ala
865 870 875 880

Tyr Val Val Leu Thr Ser Val Asn Leu Phe Ile Gly Ile Asn Gly Ser
885 890 895

Val Ala Thr Phe Val Leu Glu Leu Phe Thr Asn Asn Lys Leu Asn Asp
900 905 910

Ile Asn Asp Ile Leu Lys Ser Val Phe Leu Ile Phe Pro His Phe Cys
915 920 925

Leu Gly Arg Gly Leu Ile Asp Met Val Lys Asn Gln Ala Met Ala Asp
930 935 940

Ala Leu Glu Arg Phe Gly Glu Asn Arg Phe Val Ser Pro Leu Ser Trp
945 950 955 960

Asp Leu Val Gly Arg Asn Leu Phe Ala Met Ala Val Glu Gly Val Val
965 970 975

Phe Phe Leu Ile Thr Val Leu Ile Gln Tyr Arg Phe Phe Ile Arg Pro
980 985 990

Arg Pro Val Lys Ala Lys Leu Pro Pro Leu Asn Asp Glu Asp Glu Asp
995 1000 1005

Val Arg Arg Glu Arg Gln Arg Ile Leu Asp Gly Gly Gly Gln Asn Asp
1010 1015 1020

BNSDOCID: <WO___9748797A1_I_>

Ile Leu Glu Ile Lys Glu Leu Thr Lys Ile Tyr Arg Arg Lys Arg Lys
1025 1030 1035 1040

Pro Ala Val Asp Arg Ile Cys Ile Gly Ile Pro Pro Gly Glu Cys Phe
1045 1050 1055

Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Ser Thr Thr Phe Lys Met
1060 1065 1070

Leu Thr Gly Asp Thr Pro Val Thr Arg Gly Asp Ala Phe Leu Asn Lys
1075 1080 1085

Asn Ser Ile Leu Ser Asn Ile His Glu Val His Gln Asn Met Gly Tyr
1090 1095 1100

Cys Pro Gln Phe Asp Ala Ile Thr Glu Leu Leu Thr Gly Arg Glu His
1105 1110 1115 1120

Val Glu Phe Phe Ala Leu Leu Arg Gly Val Pro Glu Lys Glu Val Gly
1125 1130 1135

Lys Phe Gly Glu Trp Ala Ile Arg Lys Leu Gly Leu Val Lys Tyr Gly
1140 1145 1150

Glu Lys Tyr Ala Ser Asn Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser
1155 1160 1165

Thr Ala Met Ala Leu Ile Gly Gly Pro Pro Val Val Phe Leu Asp Glu
1170 1175 1180

Pro Thr Thr Gly Met Asp Pro Lys Ala Arg Arg Phe Leu Trp Asn Cys
1185 1190 1195 1200

Ala Leu Ser Ile Val Lys Glu Gly Arg Ser Val Val Leu Thr Ser His
1205 1210 1215

Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Met Ala Ile Met Val
1220 1225 1230

Asn Gly Arg Phe Arg Cys Leu Gly Ser Val Gln His Leu Lys Asn Arg
1235 1240 1245

Phe Gly Asp Gly Tyr Thr Ile Val Val Arg Ile Ala Gly Ser Asn Pro
1250 1255 1260

Asp Leu Lys Pro Val Gln Glu Phe Phe Gly Leu Ala Phe Pro Gly Ser
1265 1270 1275 1280

Val Leu Lys Glu Lys His Arg Asn Met Leu Gln Tyr Gln Leu Pro Ser
1285 1290 1295

Ser Leu Ser Ser Leu Ala Arg Ile Phe Ser Ile Leu Ser Gln Ser Lys
1300 1305 1310

Lys Arg Leu His Ile Glu Asp Tyr Ser Val Ser Gln Thr Thr Leu Asp
1315 1320 1325

Gln Val Phe Val Asn Phe Ala Lys Asp Gln Ser Asp Asp Asp His Leu
1330 1335 1340

Lys Asp Leu Ser Leu His Lys Asn Gln Thr Val Val Asp Val Ala Val
1345 1350 1355 1360

Leu Thr Ser Phe Leu Gln Asp Glu Lys Val Lys Glu Ser Tyr Val
1365 1370 1375

BNSDOCID: <WO___9748797A1_I_>

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1457 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Met Glu Glu Glu Pro Thr His Leu Pro Leu Val Val Cys Val Asp Lys
1 5 10 15

Leu Thr Lys Val Tyr Lys Asn Asp Lys Lys Leu Ala Leu Asn Lys Leu
20 25 30

Ser Leu Asn Leu Tyr Glu Asn Gln Val Val Ser Phe Leu Gly His Asn
35 40 45

Gly Ala Gly Lys Thr Thr Thr Met Ser Ile Leu Thr Gly Leu Phe Pro
50 55 60

Pro Thr Ser Gly Ser Ala Thr Ile Tyr Gly His Asp Ile Arg Thr Glu
65 70 75 80

Met Asp Glu Ile Arg Lys Asn Leu Gly Met Cys Pro Gln His Asn Val
85 90 95

Leu Phe Asp Arg Leu Thr Val Glu Glu His Leu Trp Phe Tyr Ser Arg
100 105 110

Leu Lys Ser Met Ala Gln Glu Glu Ile Arg Lys Glu Thr Asp Lys Met
115 120 125

Ile Glu Asp Leu Glu Leu Ser Asn Lys Arg His Ser Leu Val Gln Thr
130 135 140

Leu Ser Gly Gly Met Lys Arg Lys Leu Ser Val Ala Ile Ala Phe Val
145 150 155 160

Gly Gly Ser Arg Ala Ile Ile Leu Asp Glu Pro Thr Ala Gly Val Asp
165 170 175

Pro Tyr Ala Arg Arg Ala Ile Trp Asp Leu Ile Leu Lys Tyr Lys Pro
180 185 190

Gly Arg Thr Ile Leu Leu Ser Thr His His Met Asp Glu Ala Asp Leu
195 200 205

Leu Gly Asp Arg Ile Ala Ile Ile Ser His Gly Lys Leu Lys Cys Cys
210 215 220

Gly Ser Pro Leu Phe Leu Lys Gly Ala Tyr Xaa Asp Gly Tyr Arg Leu
225 230 235 240

Thr Leu Val Lys Gln Pro Ala Glu Pro Gly Thr Ser Gln Glu Pro Gly
245 250 255

Leu Ala Ser Ser Pro Ser Gly Cys Pro Arg Leu Ser Ser Cys Ser Glu
260 265 270

BNSDOCID: <WO___9748797A1_I_>

Pro Gln Val Ser Gln Phe Ile Arg Lys His Val Ala Ser Ser Leu Leu
275 280 285

Val Ser Asp Thr Ser Thr Glu Leu Ser Tyr Ile Leu Pro Ser Glu Ala
290 295 300

Val Lys Lys Gly Ala Phe Glu Arg Leu Phe Gln Gln Leu Glu His Ser
305 310 315 320

Leu Asp Ala Leu His Leu Ser Ser Phe Gly Leu Met Asp Thr Thr Leu
325 330 335

Glu Glu Val Phe Leu Lys Val Ser Glu Glu Asp Gln Ser Leu Glu Asn
340 345 350

Ser Glu Ala Asp Val Lys Glu Ser Arg Lys Asp Val Leu Pro Gly Ala
355 360 365

Glu Gly Leu Thr Ala Val Gly Gly Gln Ala Gly Asn Leu Ala Arg Cys
370 375 380

Ser Glu Leu Ala Gln Ser Gln Ala Ser Leu Gln Ser Ala Ser Ser Val
385 390 395 400

Gly Ser Ala Arg Gly Glu Glu Gly Thr Gly Tyr Ser Asp Gly Tyr Gly
405 410 415

Asp Tyr Arg Pro Leu Phe Asp Asn Leu Gln Asp Pro Asp Asn Val Ser
420 425 430

Leu Gln Glu Ala Glu Met Glu Ala Leu Ala Gln Val Gly Gln Gly Ser
435 440 445

Arg Lys Leu Glu Gly Trp Trp Leu Lys Met Arg Gln Phe His Gly Leu
450 455 460

Leu Val Lys Arg Phe His Cys Ala Arg Arg Asn Ser Lys Ala Leu Cys
465 470 475 480

Ser Gln Ile Leu Leu Pro Ala Phe Phe Val Cys Val Ala Met Thr Val
485 490 495

Ala Leu Ser Val Pro Glu Ile Gly Asp Leu Pro Pro Leu Val Leu Ser
500 505 510

Pro Ser Gln Tyr His Asn Tyr Thr Gln Pro Arg Gly Asn Phe Ile Pro
515 520 525

Tyr Ala Asn Glu Glu Arg Gln Glu Tyr Arg Leu Arg Leu Ser Pro Asp
530 535 540

Ala Ser Pro Gln Gln Leu Val Ser Thr Phe Arg Leu Pro Ser Gly Val
545 550 555 560

Gly Ala Thr Cys Val Leu Lys Ser Pro Ala Asn Gly Ser Leu Gly Pro
565 570 575

Met Leu Asn Leu Ser Ser Gly Glu Ser Arg Leu Leu Ala Ala Arg Phe
580 585 590

Phe Asp Ser Met Cys Leu Glu Ser Phe Thr Gln Gly Leu Pro Leu Ser
595 600 605

Asn Phe Val Pro Pro Pro Pro Ser Pro Ala Pro Ser Asp Ser Pro Val
610 615 620

BNSDOCID: <WO___9748797A1_I_>

Xaa Pro Asp Glu Asp Ser Leu Gln Ala Trp Asn Met Ser Leu Pro Pro
625 630 635 640

Thr Ala Gly Pro Glu Thr Trp Thr Ser Ala Pro Ser Leu Pro Arg Leu
645 650 655

Val His Glu Pro Val Arg Cys Thr Cys Ser Ala Gln Gly Thr Gly Phe
660 665 670

Ser Cys Pro Ser Ser Val Gly Gly His Pro Pro Gln Met Arg Val Val
675 680 685

Thr Gly Asp Ile Leu Thr Asp Ile Thr Gly His Asn Val Ser Glu Tyr
690 695 700

Leu Leu Phe Thr Ser Asp Arg Phe Arg Leu His Arg Tyr Gly Ala Ile
705 710 715 720

Thr Phe Gly Asn Val Gln Lys Ser Ile Pro Ala Ser Phe Gly Ala Arg
725 730 735

Val Pro Pro Met Val Arg Lys Ile Ala Val Arg Arg Val Ala Gln Val
740 745 750

Leu Tyr Asn Asn Lys Gly Tyr His Ser Met Pro Thr Tyr Leu Asn Ser
755 760 765

Leu Asn Asn Ala Ile Leu Arg Ala Asn Leu Pro Lys Ser Lys Gly Asn
770 775 780

Pro Ala Ala Tyr Xaa Ile Thr Val Thr Asn His Pro Met Asn Lys Thr
785 790 795 800

Ser Ala Ser Leu Ser Leu Asp Tyr Leu Leu Gln Gly Thr Asp Val Val
805 810 815

Ile Ala Ile Phe Ile Ile Val Ala Met Ser Phe Val Pro Ala Ser Phe
820 825 830

Val Val Phe Leu Val Ala Glu Lys Ser Thr Lys Ala Lys His Leu Gln
835 840 845

Phe Val Ser Gly Cys Asn Pro Val Ile Tyr Trp Leu Ala Asn Tyr Val
850 855 860

Trp Asp Met Leu Asn Tyr Leu Val Pro Ala Thr Cys Cys Val Ile Ile
865 870 875 880

Leu Phe Val Phe Asp Leu Pro Ala Tyr Thr Ser Pro Thr Asn Phe Pro
885 890 895

Ala Val Leu Ser Leu Phe Leu Leu Tyr Gly Trp Ser Ile Thr Pro Ile
900 905 910

Met Tyr Pro Ala Ser Phe Trp Phe Glu Val Pro Ser Ser Ala Tyr Val
915 920 925

Phe Leu Ile Val Ile Asn Leu Phe Ile Gly Ile Thr Ala Thr Val Ala
930 935 940

Thr Phe Leu Leu Gln Leu Phe Glu His Asp Lys Asp Leu Lys Val Val
945 950 955 960

Asn Ser Tyr Leu Lys Ser Cys Phe Leu Ile Phe Pro Asn Tyr Asn Leu
965 970 975

BNSDOCID: <WO___9748797A1_I_>

Gly His Gly Leu Met Glu Met Ala Tyr Asn Glu Tyr Ile Asn Glu Tyr
980 985 990

Tyr Ala Lys Ile Gly Gln Phe Asp Lys Met Lys Ser Pro Phe Glu Trp
995 1000 1005

Asp Ile Val Thr Arg Gly Leu Val Ala Met Thr Val Glu Gly Phe Val
1010 1015 1020

Gly Phe Phe Leu Thr Ile Met Cys Gln Tyr Asn Phe Leu Arg Gln Pro
1025 1030 1035 1040

Gln Arg Leu Pro Val Ser Thr Lys Pro Val Glu Asp Asp Val Asp Val
1045 1050 1055

Ala Ser Glu Arg Gln Arg Val Leu Arg Gly Asp Ala Asp Asn Asp Met
1060 1065 1070

Val Lys Ile Glu Asn Leu Thr Lys Val Tyr Lys Ser Arg Lys Ile Gly
1075 1080 1085

Arg Ile Leu Ala Val Asp Arg Leu Cys Leu Gly Val Cys Val Pro Gly
1090 1095 1100

Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Ser Thr
1105 1110 1115 1120

Phe Lys Met Leu Thr Gly Asp Glu Ser Thr Thr Gly Gly Glu Ala Phe
1125 1130 1135

Val Asn Gly His Ser Val Leu Lys Asp Leu Leu Gln Val Gln Gln Ser
1140 1145 1150

Leu Gly Tyr Cys Pro Gln Phe Asp Val Pro Val Asp Glu Leu Thr Ala
1155 1160 1165

Arg Glu His Leu Gln Leu Tyr Thr Arg Leu Arg Cys Ile Pro Trp Lys
1170 1175 1180

Asp Glu Ala Gln Val Val Lys Trp Ala Leu Glu Lys Leu Glu Leu Thr
1185 1190 1195 1200

Lys Tyr Ala Asp Lys Pro Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg
1205 1210 1215

Lys Leu Ser Thr Ala Ile Ala Leu Ile Gly Tyr Pro Ala Phe Ile Phe
1220 1225 1230

Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Lys Ala Arg Arg Phe Leu
1235 1240 1245

Trp Asn Leu Ile Leu Asp Leu Ile Lys Thr Gly Arg Ser Val Val Leu
1250 1255 1260

Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala
1265 1270 1275 1280

Ile Met Val Asn Gly Arg Leu His Cys Leu Gly Ser Ile Gln His Leu
1285 1290 1295

Lys Asn Arg Phe Gly Asp Gly Tyr Met Ile Thr Val Arg Thr Lys Ser
1300 1305 1310

Ser Gln Asn Val Lys Asp Val Val Arg Phe Phe Asn Arg Asn Phe Pro
1315 1320 1325

BNSDOCID: <WO___9748797A1_I_>

```
Glu Ala His Ala Gln Gly Lys Thr Pro Tyr Lys Val Gln Tyr Gln Leu
     1330                1335                1340

Lys Ser Glu His Ile Ser Leu Ala Gln Val Phe Ser Lys Met Glu Gln
1345                1350                1355                1360

Val Val Gly Val Leu Gly Ile Glu Asp Tyr Ser Val Ser Gln Thr Thr
                    1365                1370                1375

Leu Asp Asn Val Phe Val Asn Phe Ala Lys Lys Gln Ser Asp Asn Val
                1380                1385                1390

Glu Gln Gln Glu Ala Glu Pro Ser Ser Leu Pro Ser Pro Leu Gly Leu
            1395                1400                1405

Leu Ser Leu Leu Arg Pro Arg Pro Ala Pro Thr Glu Leu Arg Ala Leu
     1410                1415                1420

Val Ala Asp Glu Pro Glu Asp Leu Asp Thr Glu Asp Glu Gly Leu Ile
1425                1430                1435                1440

Ser Phe Glu Glu Glu Arg Ala Gln Leu Ser Phe Asn Thr Asp Thr Leu
                    1445                1450                1455

Cys
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1548 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 49..1271

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
GGCGGCTAGC GGCGAGGCCC CTTCCTGTAC CTTCAGGGAT CGGCCACC ATG TCC CAC      57
                                                      Met Ser His
                                                        1

CGG AAG TTT TCC GCC CCT CGG CAC GGA CAC CTG GGC TTC CTG CCC CAT      105
Arg Lys Phe Ser Ala Pro Arg His Gly His Leu Gly Phe Leu Pro His
  5                  10                  15

AAG AGG AGC CAC CGG CAC CGG GGC AAG GTG AAG ACG TGG CCG CGG GAT      153
Lys Arg Ser His Arg His Arg Gly Lys Val Lys Thr Trp Pro Arg Asp
 20                  25                  30                  35

GAC CCC AGC CAG CCC GTG CAC CTC ACG GCC TTC CTG GGC TAC AAG GCG      201
Asp Pro Ser Gln Pro Val His Leu Thr Ala Phe Leu Gly Tyr Lys Ala
                 40                  45                  50

GGC ATG ACC CAC ACC CTG CGG GAG GTG CAC CGG CCG GGG CTC AAA ATT      249
Gly Met Thr His Thr Leu Arg Glu Val His Arg Pro Gly Leu Lys Ile
            55                  60                  65
```


BNSDOCID: <WO___9748797A1_I_>

```
TCC AAA CGG GAG GAG GTG GAG GCG GTG ACA ATT GTA GAA ACG CCG CCC      297
Ser Lys Arg Glu Glu Val Glu Ala Val Thr Ile Val Glu Thr Pro Pro
            70                  75                  80

CTA GTG GTG GTG GGC GTG GTG GGC TAC GTG GCC ACC CCT CGA GGT CTC      345
Leu Val Val Val Gly Val Val Gly Tyr Val Ala Thr Pro Arg Gly Leu
        85                  90                  95

CGG AGC TTC AAG ACC ATC TTT GCA GAA CAC CTC AGT GAT GAG TGC CGG      393
Arg Ser Phe Lys Thr Ile Phe Ala Glu His Leu Ser Asp Glu Cys Arg
100                 105                 110                 115

CGC CGA TTC TAC AAG GAC TGG CAC AAG AGC AAG AAG AAA GCC TTC ACC      441
Arg Arg Phe Tyr Lys Asp Trp His Lys Ser Lys Lys Lys Ala Phe Thr
                120                 125                 130

AAG GCC TGC AAG AGG TGG CGG GAC ACA GAC GGG AAA AAG CAG CTA CAG      489
Lys Ala Cys Lys Arg Trp Arg Asp Thr Asp Gly Lys Lys Gln Leu Gln
            135                 140                 145

AAG GAC TTC GCC GCC ATG AAG AAG TAC TGC AAG GTC ATT CGG GTC ATT      537
Lys Asp Phe Ala Ala Met Lys Lys Tyr Cys Lys Val Ile Arg Val Ile
        150                 155                 160

GTC CAC ACT CAG ATG AAA CTG CTG CCC TTC CGG CAG AAG AAG GCC CAC      585
Val His Thr Gln Met Lys Leu Leu Pro Phe Arg Gln Lys Lys Ala His
    165                 170                 175

ATC ATG GAG ATC CAG CTG AAC GGT GGC ACG GTG GCC GAG AAG GTG GCC      633
Ile Met Glu Ile Gln Leu Asn Gly Gly Thr Val Ala Glu Lys Val Ala
180                 185                 190                 195

TGG GCC CAG GCC CGG CTG GAG AAG CAG GTG CCC GTG CAC AGC GTG TTC      681
Trp Ala Gln Ala Arg Leu Glu Lys Gln Val Pro Val His Ser Val Phe
                200                 205                 210

AGC CAG AGT GAG GTC ATT GAT GTC ATT GCT GTC ACC AAG GGT CGA GGC      729
Ser Gln Ser Glu Val Ile Asp Val Ile Ala Val Thr Lys Gly Arg Gly
            215                 220                 225

GTC AAA GGG GTC ACA AGC CGC TGG CAT ACC AAG AAG CTG CCG CGC AAG      777
Val Lys Gly Val Thr Ser Arg Trp His Thr Lys Lys Leu Pro Arg Lys
        230                 235                 240

ACC CAT AAG GGC CTG CGC AAG GTG GCC TGC ATT GGC GCC TGG CAC CCC      825
Thr His Lys Gly Leu Arg Lys Val Ala Cys Ile Gly Ala Trp His Pro
    245                 250                 255

GCC CGC GTG GGC TGC TCC ATT GCT CGG GCC GGG CAG AAG GGC TAT CAC      873
Ala Arg Val Gly Cys Ser Ile Ala Arg Ala Gly Gln Lys Gly Tyr His
260                 265                 270                 275

CAC CGC ACG GAG CTC AAC AAG AAG ATC TTC CGC ATC GGC AGG GGC CCG      921
His Arg Thr Glu Leu Asn Lys Lys Ile Phe Arg Ile Gly Arg Gly Pro
                280                 285                 290

CAC ATG GAG GAC GGG AAG CTG GTG AAG AAC AAT GCA TCC ACC AGC TAC      969
His Met Glu Asp Gly Lys Leu Val Lys Asn Asn Ala Ser Thr Ser Tyr
            295                 300                 305

GAC GTG ACT GCC AAG TCC ATC ACA CCG CTG GGT GGC TTC CCC CAC TAC     1017
Asp Val Thr Ala Lys Ser Ile Thr Pro Leu Gly Gly Phe Pro His Tyr
        310                 315                 320
```


BNSDOCID: <WO___9748797A1_I_>

```
GGG GAA GTG AAC AAC GAC TTC GTC ATG CTG AAG GGT TGT ATT GCT GGT      1065
Gly Glu Val Asn Asn Asp Phe Val Met Leu Lys Gly Cys Ile Ala Gly
    325                 330                 335

ACC AAG AAG CGG GTC ATT ACG CTG AGA AAG TCC CTC CTG GTG CAT CAC      1113
Thr Lys Lys Arg Val Ile Thr Leu Arg Lys Ser Leu Leu Val His His
340                 345                 350                 355

AGT CGC CAA GCC GTG GAG AAT ATT GAG CTC AAG TTC ATT GAC ACC ACC      1161
Ser Arg Gln Ala Val Glu Asn Ile Glu Leu Lys Phe Ile Asp Thr Thr
                360                 365                 370

TCC AAG TTC GGC CAT GGC CGC TTC CAG ACA GCC CAA GAG AAG AGG GCC      1209
Ser Lys Phe Gly His Gly Arg Phe Gln Thr Ala Gln Glu Lys Arg Ala
            375                 380                 385

TTC ATG GGC CCC CAA AAG AAG CAT CTG GAG AAG GAA ACG CCG GAG ACC      1257
Phe Met Gly Pro Gln Lys Lys His Leu Glu Lys Glu Thr Pro Glu Thr
        390                 395                 400

TCG GGA GAC TTG TA GGCTGTGTGG GGTGGATGAA CCCTGAAGCG CACCGCACTG       1311
Ser Gly Asp Leu
    405

TCTGCCCCAA TGTCTAACAA AGGCCGGAGG CGACTCTTCC TGCGAGGTCT CAGAGCGCTG    1371

TGTAACCGCC CAAGGGGTTC ACCTTGCCTG CTGCCTAGAC AAAGCCGATT CATTAAGACA    1431

GGGGAATTGC AATAGAGAAA GAGTAATTCA CACAGAGCTG GCTGTGCGGG AGACCGGAGT    1491

TTTATGTTTT ATTATTACTC AAATCGATCT CTTTGAGCAA AAAAAAAAAA AAAAAAA       1548
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 407 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
Met Ser His Arg Lys Phe Ser Ala Pro Arg His Gly His Leu Gly Phe
  1               5                  10                  15

Leu Pro His Lys Arg Ser His Arg His Arg Gly Lys Val Lys Thr Trp
            20                  25                  30

Pro Arg Asp Asp Pro Ser Gln Pro Val His Leu Thr Ala Phe Leu Gly
        35                  40                  45

Tyr Lys Ala Gly Met Thr His Thr Leu Arg Glu Val His Arg Pro Gly
    50                  55                  60

Leu Lys Ile Ser Lys Arg Glu Glu Val Glu Ala Val Thr Ile Val Glu
65                  70                  75                  80

Thr Pro Pro Leu Val Val Val Gly Val Val Gly Tyr Val Ala Thr Pro
                85                  90                  95

Arg Gly Leu Arg Ser Phe Lys Thr Ile Phe Ala Glu His Leu Ser Asp
            100                 105                 110
```


BNSDOCID: <WO___9748797A1_I_>

```
Glu Cys Arg Arg Arg Phe Tyr Lys Asp Trp His Lys Ser Lys Lys Lys
        115                 120                 125

Ala Phe Thr Lys Ala Cys Lys Arg Trp Arg Asp Thr Asp Gly Lys Lys
    130                 135                 140

Gln Leu Gln Lys Asp Phe Ala Ala Met Lys Lys Tyr Cys Lys Val Ile
145                 150                 155                 160

Arg Val Ile Val His Thr Gln Met Lys Leu Leu Pro Phe Arg Gln Lys
                165                 170                 175

Lys Ala His Ile Met Glu Ile Gln Leu Asn Gly Gly Thr Val Ala Glu
            180                 185                 190

Lys Val Ala Trp Ala Gln Ala Arg Leu Glu Lys Gln Val Pro Val His
        195                 200                 205

Ser Val Phe Ser Gln Ser Glu Val Ile Asp Val Ile Ala Val Thr Lys
    210                 215                 220

Gly Arg Gly Val Lys Gly Val Thr Ser Arg Trp His Thr Lys Lys Leu
225                 230                 235                 240

Pro Arg Lys Thr His Lys Gly Leu Arg Lys Val Ala Cys Ile Gly Ala
                245                 250                 255

Trp His Pro Ala Arg Val Gly Cys Ser Ile Ala Arg Ala Gly Gln Lys
            260                 265                 270

Gly Tyr His His Arg Thr Glu Leu Asn Lys Lys Ile Phe Arg Ile Gly
        275                 280                 285

Arg Gly Pro His Met Glu Asp Gly Lys Leu Val Lys Asn Asn Ala Ser
    290                 295                 300

Thr Ser Tyr Asp Val Thr Ala Lys Ser Ile Thr Pro Leu Gly Gly Phe
305                 310                 315                 320

Pro His Tyr Gly Glu Val Asn Asn Asp Phe Val Met Leu Lys Gly Cys
                325                 330                 335

Ile Ala Gly Thr Lys Lys Arg Val Ile Thr Leu Arg Lys Ser Leu Leu
            340                 345                 350

Val His His Ser Arg Gln Ala Val Glu Asn Ile Glu Leu Lys Phe Ile
        355                 360                 365

Asp Thr Thr Ser Lys Phe Gly His Gly Arg Phe Gln Thr Ala Gln Glu
    370                 375                 380

Lys Arg Ala Phe Met Gly Pro Gln Lys Lys His Leu Glu Lys Glu Thr
385                 390                 395                 400

Pro Glu Thr Ser Gly Asp Leu
                405
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 403 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

BNSDOCID: <WO___9748797A1_I_>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Ser His Arg Lys Phe Ser Ala Pro Arg His Gly Ser Leu Gly Phe
1 5 10 15

Leu Pro Arg Lys Arg Ser Ser Arg His Arg Gly Lys Val Lys Ser Phe
20 25 30

Pro Lys Asp Asp Pro Ser Lys Pro Val His Leu Thr Ala Phe Leu Gly
35 40 45

Tyr Lys Ala Gly Met Thr His Ile Val Arg Glu Val Asp Arg Pro Gly
50 55 60

Ser Lys Val Asn Lys Lys Glu Val Val Glu Ala Val Thr Ile Val Glu
65 70 75 80

Thr Pro Pro Met Val Val Val Gly Ile Val Gly Tyr Val Glu Thr Pro
85 90 95

Arg Gly Leu Arg Thr Phe Lys Thr Val Phe Ala Glu His Ile Ser Asp
100 105 110

Glu Cys Lys Arg Arg Phe Tyr Lys Asn Trp His Lys Ser Lys Lys Lys
115 120 125

Ala Phe Thr Lys Tyr Cys Lys Lys Trp Gln Asp Glu Asp Gly Lys Lys
130 135 140

Gln Leu Glu Lys Asp Phe Ser Ser Met Lys Lys Tyr Cys Gln Val Ile
145 150 155 160

Arg Val Ile Ala His Thr Gln Met Arg Leu Leu Pro Leu Arg Gln Lys
165 170 175

Lys Ala His Leu Met Glu Ile Gln Val Asn Gly Gly Thr Val Ala Glu
180 185 190

Lys Leu Asp Trp Ala Arg Glu Arg Leu Glu Gln Gln Val Pro Val Asn
195 200 205

Gln Val Phe Gly Gln Asp Glu Met Ile Asp Val Ile Gly Val Thr Lys
210 215 220

Gly Lys Gly Tyr Lys Gly Val Thr Ser Arg Trp His Thr Lys Lys Leu
225 230 235 240

Pro Arg Lys Thr His Arg Gly Leu Arg Lys Val Ala Cys Ile Gly Ala
245 250 255

Trp His Pro Ala Arg Val Ala Phe Ser Val Ala Arg Ala Gly Gln Lys
260 265 270

Gly Tyr His His Arg Thr Glu Ile Asn Lys Lys Ile Tyr Lys Ile Gly
275 280 285

Gln Gly Tyr Leu Ile Lys Asp Gly Lys Leu Ile Lys Asn Asn Ala Ser
290 295 300

Thr Asp Tyr Asp Leu Ser Asp Lys Ser Ile Asn Pro Leu Gly Gly Phe
305 310 315 320

BNSDOCID: <WO___9748797A1_I_>

Val His Tyr Gly Glu Val Thr Asn Asp Phe Val Met Leu Lys Gly Cys
325 330 335

Val Val Gly Thr Lys Lys Arg Val Leu Thr Leu Arg Lys Ser Leu Leu
340 345 350

Val Gln Thr Lys Arg Arg Ala Leu Glu Lys Ile Asp Leu Lys Phe Ile
355 360 365

Asp Thr Thr Ser Lys Phe Gly His Gly Arg Phe Gln Thr Met Glu Glu
370 375 380

Lys Lys Ala Phe Met Gly Pro Leu Lys Lys Asp Arg Ile Ala Lys Glu
385 390 395 400

Glu Gly Ala

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 403 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Met Ser His Arg Lys Phe Ser Ala Pro Arg His Gly Ser Leu Gly Phe
1 5 10 15

Leu Pro Arg Lys Arg Ser Ser Arg His Arg Gly Lys Val Lys Ser Phe
20 25 30

Pro Lys Asp Asp Ser Ser Lys Pro Val His Leu Thr Ala Phe Leu Gly
35 40 45

Tyr Lys Ala Gly Met Thr His Ile Val Arg Glu Val Asp Arg Pro Gly
50 55 60

Ser Lys Val Asn Lys Lys Glu Val Val Glu Ala Val Thr Ile Val Glu
65 70 75 80

Thr Pro Pro Met Val Ile Val Gly Ile Val Gly Tyr Val Glu Thr Pro
85 90 95

Arg Gly Leu Arg Thr Phe Lys Thr Ile Phe Ala Glu His Ile Ser Asp
100 105 110

Glu Cys Lys Arg Arg Phe Tyr Lys Asn Trp His Lys Ser Lys Lys Lys
115 120 125

Ala Phe Thr Lys Tyr Cys Lys Lys Trp Gln Asp Ala Asp Gly Lys Lys
130 135 140

Gln Leu Glu Arg Asp Phe Ser Ser Met Lys Lys Tyr Cys Gln Val Ile
145 150 155 160

Arg Val Ile Ala His Thr Gln Met Arg Leu Leu Pro Leu Arg Gln Lys
165 170 175

BNSDOCID: <WO___9748797A1_I_>

Lys Ala His Leu Met Glu Val Gln Val Asn Gly Gly Thr Val Ala Glu
180 185 190

Lys Leu Asp Trp Ala Arg Glu Arg Leu Glu Gln Gln Val Pro Val Asn
195 200 205

Gln Val Phe Gly Gln Asp Glu Met Ile Asp Val Ile Gly Val Thr Lys
210 215 220

Gly Lys Gly Tyr Lys Gly Val Thr Ser Arg Trp His Thr Lys Lys Leu
225 230 235 240

Pro Arg Lys Thr His Arg Gly Leu Arg Lys Val Ala Cys Ile Gly Ala
245 250 255

Trp His Pro Ala Arg Val Ala Phe Ser Val Ala Arg Ala Gly Gln Lys
260 265 270

Gly Tyr His His Arg Thr Glu Ile Asn Lys Lys Ile Tyr Lys Ile Gly
275 280 285

Gln Gly Tyr Leu Ile Lys Asp Gly Lys Leu Ile Lys Asn Asn Ala Ser
290 295 300

Thr Asp Tyr Asp Leu Ser Asp Lys Ser Ile Asn Pro Leu Gly Gly Phe
305 310 315 320

Val His Tyr Gly Glu Val Thr Asn Asp Phe Val Met Leu Lys Gly Cys
325 330 335

Val Val Gly Thr Lys Lys Arg Val Leu Thr Leu Arg Lys Ser Leu Leu
340 345 350

Val Gln Thr Lys Arg Arg Ala Leu Glu Lys Ile Asp Leu Lys Phe Ile
355 360 365

Asp Thr Thr Ser Lys Phe Gly His Gly Arg Phe Gln Thr Val Glu Glu
370 375 380

Lys Lys Ala Phe Met Gly Pro Leu Lys Lys Asp Arg Ile Ala Lys Glu
385 390 395 400

Glu Gly Ala

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 403 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Ser His Arg Lys Phe Ser Ala Pro Arg His Gly Ser Leu Gly Phe
1 5 10 15

Leu Pro Arg Lys Arg Ser Ser Arg His Arg Gly Lys Val Lys Ser Phe
20 25 30

BNSDOCID: <WO___9748797A1_I_>

Pro Lys Asp Asp Ala Ser Lys Pro Val His Leu Thr Ala Phe Leu Gly
35 40 45

Tyr Lys Ala Gly Met Thr His Ile Val Arg Glu Val Asp Arg Pro Gly
50 55 60

Ser Lys Val Asn Lys Lys Glu Val Val Glu Ala Val Thr Ile Val Glu
65 70 75 80

Thr Pro Pro Met Val Val Val Gly Ile Val Gly Tyr Val Glu Thr Pro
85 90 95

Arg Gly Leu Arg Thr Phe Lys Thr Val Phe Ala Glu His Ile Ser Asp
100 105 110

Glu Cys Lys Arg Arg Phe Tyr Lys Asn Trp His Lys Ser Lys Lys Lys
115 120 125

Ala Phe Thr Lys Tyr Cys Lys Lys Trp Gln Asp Asp Thr Gly Lys Lys
130 135 140

Gln Leu Glu Lys Asp Phe Asn Ser Met Lys Lys Tyr Cys Gln Val Ile
145 150 155 160

Arg Ile Ile Ala His Thr Gln Met Arg Leu Leu Pro Leu Arg Gln Lys
165 170 175

Lys Ala His Leu Met Glu Ile Gln Val Asn Gly Gly Thr Val Ala Glu
180 185 190

Lys Leu Asp Trp Ala Arg Glu Arg Leu Glu Gln Gln Val Pro Val Ser
195 200 205

Gln Val Phe Gly Gln Asp Glu Met Ile Asp Val Ile Gly Val Thr Lys
210 215 220

Gly Lys Gly Tyr Lys Gly Val Thr Ser Arg Trp His Thr Lys Lys Leu
225 230 235 240

Pro Arg Lys Thr His Arg Gly Leu Arg Lys Val Ala Cys Ile Gly Ala
245 250 255

Trp His Pro Ala Arg Val Ala Phe Thr Val Ala Arg Ala Gly Gln Lys
260 265 270

Gly Tyr His His Arg Thr Glu Ile Asn Lys Lys Ile Tyr Lys Ile Gly
275 280 285

Gln Gly Tyr Leu Ile Lys Asp Gly Lys Leu Ile Lys Asn Asn Ala Ser
290 295 300

Thr Asp Tyr Asp Leu Ser Asp Lys Ser Ile Asn Pro Leu Gly Gly Phe
305 310 315 320

Val His Tyr Gly Glu Val Thr Asn Asp Phe Ile Met Leu Lys Gly Cys
325 330 335

Val Val Gly Thr Lys Lys Arg Val Leu Thr Leu Arg Lys Ser Leu Leu
340 345 350

Val Gln Thr Lys Arg Arg Ala Leu Glu Lys Ile Asp Leu Lys Phe Ile
355 360 365

Asp Thr Thr Ser Lys Phe Gly His Gly Arg Phe Gln Thr Met Glu Glu
370 375 380

BNSDOCID: <WO___9748797A1_I_>

```
Lys Lys Ala Phe Met Gly Pro Leu Lys Lys Asp Arg Ile Ala Lys Glu
385                 390                 395                 400

Glu Gly Ala
```

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 468 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..357

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```
CGG GAC ACC AAG TTT AGG GAG GAC TGC CCG CCG GAT CGC GAG GAA CTG      48
Arg Asp Thr Lys Phe Arg Glu Asp Cys Pro Pro Asp Arg Glu Glu Leu
 1               5                  10                  15

GGC CGC CAC AGC TGG GCT GTC CTC CAC ACC CTG GCC GCC TAC TAC CCC      96
Gly Arg His Ser Trp Ala Val Leu His Thr Leu Ala Ala Tyr Tyr Pro
            20                  25                  30

GAC CTG CCC ACC CCA GAA CAG CAG CAA GAC ATG GCC CAG TTC ATA CAT     144
Asp Leu Pro Thr Pro Glu Gln Gln Gln Asp Met Ala Gln Phe Ile His
        35                  40                  45

TTA TTT TCT AAG TTT TAC CCC TGT GAG GAG TGT GCT GAA GAC CTA AGA     192
Leu Phe Ser Lys Phe Tyr Pro Cys Glu Glu Cys Ala Glu Asp Leu Arg
    50                  55                  60

AAA AGG CTG TGC AGG AAC CAC CCA GAC ACC CGC ACC CGG GCA TGC TTC     240
Lys Arg Leu Cys Arg Asn His Pro Asp Thr Arg Thr Arg Ala Cys Phe
65                  70                  75                  80

ACA CAG TGG CTG TGC CAC CTG CAC AAT GAA GTG AAC CGC AAG CTG GGC     288
Thr Gln Trp Leu Cys His Leu His Asn Glu Val Asn Arg Lys Leu Gly
                85                  90                  95

AAG CCT GAC TTC GAC TGC TCA AAA GTG GAT GAG CGC TGG CGC GAC GGC     336
Lys Pro Asp Phe Asp Cys Ser Lys Val Asp Glu Arg Trp Arg Asp Gly
            100                 105                 110

TGG AAG GAT GGC TCC TGT GAC TAGAGGGTGG TCAGCCAGAG CTCATGGGAC       387
Trp Lys Asp Gly Ser Cys Asp
        115

AGCTAGCCAG GCATGGTTGG ATAGGGGCAG GGCACTCATT AAAGTGCATC ACAGCCAGAA   447

AAAAAAAAAA AAAAAAAAAA A                                            468
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 119 amino acids
(B) TYPE: amino acid

BNSDOCID: <WO___9748797A1_I_>

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

```
Arg Asp Thr Lys Phe Arg Glu Asp Cys Pro Pro Asp Arg Glu Glu Leu
 1               5                  10                  15

Gly Arg His Ser Trp Ala Val Leu His Thr Leu Ala Ala Tyr Tyr Pro
            20                  25                  30

Asp Leu Pro Thr Pro Glu Gln Gln Gln Asp Met Ala Gln Phe Ile His
        35                  40                  45

Leu Phe Ser Lys Phe Tyr Pro Cys Glu Glu Cys Ala Glu Asp Leu Arg
    50                  55                  60

Lys Arg Leu Cys Arg Asn His Pro Asp Thr Arg Thr Arg Ala Cys Phe
65                  70                  75                  80

Thr Gln Trp Leu Cys His Leu His Asn Glu Val Asn Arg Lys Leu Gly
                85                  90                  95

Lys Pro Asp Phe Asp Cys Ser Lys Val Asp Glu Arg Trp Arg Asp Gly
            100                 105                 110

Trp Lys Asp Gly Ser Cys Asp
        115
```

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 125 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```
Met Arg Thr Gln Gln Lys Arg Asp Ile Lys Phe Arg Glu Asp Cys Pro
1               5                  10                  15

Gln Asp Arg Glu Glu Leu Gly Arg Asn Thr Trp Ala Phe Leu His Thr
            20                  25                  30

Leu Ala Ala Tyr Tyr Pro Asp Met Pro Thr Pro Glu Gln Gln Gln Asp
        35                  40                  45

Met Ala Gln Phe Ile His Ile Phe Ser Lys Phe Tyr Pro Cys Glu Glu
    50                  55                  60

Cys Ala Glu Asp Ile Arg Lys Arg Ile Asp Arg Ser Gln Pro Asp Thr
65                  70                  75                  80

Ser Thr Arg Val Ser Phe Ser Gln Trp Leu Cys Arg Leu His Asn Glu
                85                  90                  95
```


BNSDOCID: <WO___9748797A1_I_>

Val Asn Arg Lys Leu Gly Lys Pro Asp Phe Asp Cys Ser Arg Val Asp
100 105 110

Glu Arg Trp Arg Asp Gly Trp Lys Asp Gly Ser Cys Asp
115 120 125

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

TGACGCCGTG CCCATCCAGT 20

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CAGCGTGGTG TTATGTTCCT 20

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TTGGGCCTGT GCTGAACTAC 20

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

BNSDOCID: <WO___9748797A1_I_>

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CGGCAAGCTG GTGATTAACA 20

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CGGCAGAGGA TGCTGTGT 18

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GCGGAGCCAC CTTCATCA 18

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GACGCTGGTG AAGGAGC 17

BNSDOCID: <WO___9748797A1_I_>

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

TCGCTGACCG CCAGGAT 17

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CTGTCGGGAA GGTCTCACTG 20

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

GTTCACCGCC TTGGAGGATT 20

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

BNSDOCID: <WO___9748797A1_I_>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GTGTGGGGAA GACCTGTCTG 20

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

AGGAGGCCTT GTTGGTGACA 20

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

ACGGACACCT GGGCTTC 17

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

AAACGGGAGG AGGTGGA 17

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

BNSDOCID: <WO___9748797A1_I_>

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

TGTGGCTATG AGCTGTTCTC 20

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

GCAGTCCCGA TTCTGAATAT 20

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

CATTGCCCGT GCTGTCGTG 19

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

CATCGCCGCC TCCTTCATG 19

(2) INFORMATION FOR SEQ ID NO:54:

BNSDOCID: <WO___9748797A1_I_>

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

GCGGAGCCAC CTTCATCA 18

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GACGCTGGTG AAGGAGC 17

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

ATCCTGGCGG TCAGCGA 17

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

BNSDOCID: <WO___9748797A1_I_>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

AGGGATTCGA CATTGCC 17

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

CTTCAGAGAC TCAGGGGCAT 20

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

GCCTGTCATC GCTCTAG 17

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

CAGTCGCAGG CCCTGCA 17

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

BNSDOCID: <WO___9748797A1_I_>

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

GAGGACGCGC CAACATC 17

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CGGCAGTAGT GGCAGTG 17

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CCTGCCTCGC TTGCTCCTGC 20

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

CGGGCAGCCG CAGGCCGCAT 20

(2) INFORMATION FOR SEQ ID NO:65:

BNSDOCID: <WO___9748797A1_I_>

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

CCTGCAACGG CCATGCCCGC 20

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

GCATCCCCGG CGGGCACCCA 20

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GTTCGTACGA GAATCGCT 18

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Kozak Initiation Sequence"

BNSDOCID: <WO___9748797A1_I_>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

CCACCATGT 9

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

TGGCCCAGTT CATACATTTA 20

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

TTACCCCTGT GAGGAGTGTG 20

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

His Arg Asp Leu Lys Pro Glu Asn
1 5

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

BNSDOCID: <WO___9748797A1_I_>

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

GTCCTTCTTG CAGAACT 17

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

AGACAGCCCA AGAGAAGAGG 20

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6525 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 573..5684

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

CACATAAAAT ACACCGCCCC GGCGCCCAGG CTCGGTGCTG GAGAGTCATG CCTGTGAGCC 60

CTGGGCACCT CCTGATGTCC TGCGAGGTCA CGGTGTTCCC AAACCTCAGG GTTGCCCTGC 120

CCCACTCCAG AGGCTCTCAG GCCCCACCCC GGAGCCCTCT GTGCGGAGCC GCCTCCTCCT 180

GGCCAGTTCC CCAGTAGTCC TGAAGGGAGA CCTGCTGTGT GGAGCCTCTT CTGGGACCCA 240

GCCATGAGTG TGGAGCTGAG CAACTGAACC TGAAACTCTT CCACTGTGAG TCAAGGAGGC 300

TTTTCCGCAC ATGAAGGACG CTGAGCGGGA AGGACTCCTC TCTGCCTGCA GTTGTAGCGA 360

GTGGACCAGC ACCAGGGGCT CTCTAGACTG CCCCTCCTCC ATCGCCTTCC CTGCCTCTCC 420

AGGACAGAGC AGCCACGTCT GCACACCTCG CCCTCTTTAC ACTCAGTTTT CAGAGCACGT 480

TTCTCCTATT TCCTGCGGGT TGCAGCGCCT ACTTGAACTT ACTCAGACCA CCTACTTCTC 540

BNSDOCID: <WO___9748797A1_I_>

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TAGCAGCACT GGGCGTCCCT TTCAGCAAGA CG ATG GCT GTG CTC AGG CAG CTG          593
                                    Met Ala Val Leu Arg Gln Leu
                                     1               5

GCG CTC CTC CTC TGG AAG AAC TAC ACC CTG CAG AAG CGG AAG GTC CTG          641
Ala Leu Leu Leu Trp Lys Asn Tyr Thr Leu Gln Lys Arg Lys Val Leu
         10                  15                  20

GTG ACG GTC CTG GAA CTC TTC CTG CCA TTG CTG TTT TCT GGG ATC CTC          689
Val Thr Val Leu Glu Leu Phe Leu Pro Leu Leu Phe Ser Gly Ile Leu
     25                  30                  35

ATC TGG CTC CGC TTG AAG ATT CAG TCG GAA AAT GTG CCC AAC GCC ACC          737
Ile Trp Leu Arg Leu Lys Ile Gln Ser Glu Asn Val Pro Asn Ala Thr
 40                  45                  50                  55

ATC TAC CCG GGC CAG TCC ATC CAG GAG CTG CCT CTG TTC TTC ACC TTC          785
Ile Tyr Pro Gly Gln Ser Ile Gln Glu Leu Pro Leu Phe Phe Thr Phe
                 60                  65                  70

CCT CCG CCA GGA GAC ACC TGG GAG CTT GCC TAC ATC CCT TCT CAC AGT          833
Pro Pro Pro Gly Asp Thr Trp Glu Leu Ala Tyr Ile Pro Ser His Ser
             75                  80                  85

GAC GCT GCC AAG GCC GTC ACT GAG ACA GTG CGC AGG GCA CTT GTG ATC          881
Asp Ala Ala Lys Ala Val Thr Glu Thr Val Arg Arg Ala Leu Val Ile
         90                  95                 100

AAC ATG CGA GTG CGC GGC TTT CCC TCC GAG AAG GAC TTT GAG GAC TAC          929
Asn Met Arg Val Arg Gly Phe Pro Ser Glu Lys Asp Phe Glu Asp Tyr
    105                 110                 115

ATT AGG TAC GAC AAC TGC TCG TCC AGC GTG CTG GCC GCC GTG GTC TTC          977
Ile Arg Tyr Asp Asn Cys Ser Ser Ser Val Leu Ala Ala Val Val Phe
120                 125                 130                 135

GAG CAC CCC TTC AAC CAC AGC AAG GAG CCC CTG CCG CTG GCG GTG AAA         1025
Glu His Pro Phe Asn His Ser Lys Glu Pro Leu Pro Leu Ala Val Lys
                140                 145                 150

TAT CAC CTA CGG TTC AGT TAC ACA CGG AGA AAT TAC ATG TGG ACC CAA         1073
Tyr His Leu Arg Phe Ser Tyr Thr Arg Arg Asn Tyr Met Trp Thr Gln
            155                 160                 165

ACA GGC TCC TTT TTC CTG AAA GAG ACA GAA GGC TGG CAC ACT ACT TCC         1121
Thr Gly Ser Phe Phe Leu Lys Glu Thr Glu Gly Trp His Thr Thr Ser
        170                 175                 180

CTT TTC CCG CTT TTC CCA AAC CCA GGA CCA AGG GAA CTA ACA TCC CCT         1169
Leu Phe Pro Leu Phe Pro Asn Pro Gly Pro Arg Glu Leu Thr Ser Pro
    185                 190                 195

GAT GGC GGA GAA CCT GGG TAC ATC CGG GAA GGC TTC CTG GCC GTG CAG         1217
Asp Gly Gly Glu Pro Gly Tyr Ile Arg Glu Gly Phe Leu Ala Val Gln
200                 205                 210                 215

CAT GCT GTG GAC CGG GCC ATC ATG GAG TAC CAT GCC GAT GCC GCC ACA         1265
His Ala Val Asp Arg Ala Ile Met Glu Tyr His Ala Asp Ala Ala Thr
                220                 225                 230

CGC CAG CTG TTC CAG AGA CTG ACG GTG ACC ATC AAG AGG TTC CCG TAC         1313
Arg Gln Leu Phe Gln Arg Leu Thr Val Thr Ile Lys Arg Phe Pro Tyr
            235                 240                 245
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BNSDOCID: <WO___9748797A1_I_>

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CCG CCG TTC ATC GCA GAC CCC TTC CTC GTG GCC ATC CAG TAC CAG CTG      1361
Pro Pro Phe Ile Ala Asp Pro Phe Leu Val Ala Ile Gln Tyr Gln Leu
        250                 255                 260

CCC CTG CTG CTG CTG CTC AGC TTC ACC TAC ACC GCG CTC ACC ATT GCC      1409
Pro Leu Leu Leu Leu Leu Ser Phe Thr Tyr Thr Ala Leu Thr Ile Ala
    265                 270                 275

CGT GCT GTC GTG CAG GAG AAG GAA AGG AGG CTG AAG GAG TAC ATG CGC      1457
Arg Ala Val Val Gln Glu Lys Glu Arg Arg Leu Lys Glu Tyr Met Arg
280                 285                 290                 295

ATG ATG GGG CTC AGC AGC TGG CTG CAC TGG AGT GCC TGG TTC CTC TTG      1505
Met Met Gly Leu Ser Ser Trp Leu His Trp Ser Ala Trp Phe Leu Leu
                300                 305                 310

TTC TTC CTC TTC CTC CTC ATC GCC GCC TCC TTC ATG ACC CTG CTC TTC      1553
Phe Phe Leu Phe Leu Leu Ile Ala Ala Ser Phe Met Thr Leu Leu Phe
            315                 320                 325

TGT GTC AAG GTG AAG CCA AAT GTA GCC GTG CTG TCC CGC AGC GAC CCC      1601
Cys Val Lys Val Lys Pro Asn Val Ala Val Leu Ser Arg Ser Asp Pro
        330                 335                 340

TCC CTG GTG CTC GCC TTC CTG CTG TGC TTC GCC ATC TCT ACC ATC TCC      1649
Ser Leu Val Leu Ala Phe Leu Leu Cys Phe Ala Ile Ser Thr Ile Ser
    345                 350                 355

TTC AGC TTC ATG GTC AGC ACC TTC TTC AGC AAA GCC AAC ATG GCA GCA      1697
Phe Ser Phe Met Val Ser Thr Phe Phe Ser Lys Ala Asn Met Ala Ala
360                 365                 370                 375

GCC TTC GGA GGC TTC CTC TAC TTC TTC ACC TAC ATC CCC TAC TTC TTC      1745
Ala Phe Gly Gly Phe Leu Tyr Phe Phe Thr Tyr Ile Pro Tyr Phe Phe
                380                 385                 390

GTG GCC CCT CGG TAC AAC TGG ATG ACT CTG AGC CAG AAG CTC TGC TCC      1793
Val Ala Pro Arg Tyr Asn Trp Met Thr Leu Ser Gln Lys Leu Cys Ser
            395                 400                 405

TGC CTC CTG TCT AAT GTC GCC ATG GCA ATG GGA GCC CAG CTC ATT GGG      1841
Cys Leu Leu Ser Asn Val Ala Met Ala Met Gly Ala Gln Leu Ile Gly
        410                 415                 420

AAA TTT GAG GCG AAA GGC ATG GGC ATC CAG TGG CGA GAC CTC CTG AGT      1889
Lys Phe Glu Ala Lys Gly Met Gly Ile Gln Trp Arg Asp Leu Leu Ser
    425                 430                 435

CCC GTC AAC GTG GAC GAC GAC TTC TGC TTC GGG CAG GTG CTG GGG ATG      1937
Pro Val Asn Val Asp Asp Asp Phe Cys Phe Gly Gln Val Leu Gly Met
440                 445                 450                 455

CTG CTG CTG GAC TCT GTG CTC TAT GGC CTG GTG ACC TGG TAC ATG GAG      1985
Leu Leu Leu Asp Ser Val Leu Tyr Gly Leu Val Thr Trp Tyr Met Glu
                460                 465                 470

GCC GTC TTC CCA GGG CAG TTC GGC GTG CCT CAG CCC TGG TAC TTC TTC      2033
Ala Val Phe Pro Gly Gln Phe Gly Val Pro Gln Pro Trp Tyr Phe Phe
            475                 480                 485

ATC ATG CCC TCC TAT TGG TGT GGG AAG CCA AGG GCG GTT GCA GGG AAG      2081
Ile Met Pro Ser Tyr Trp Cys Gly Lys Pro Arg Ala Val Ala Gly Lys
        490                 495                 500
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BNSDOCID: <WO___9748797A1_I_>

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GAG GAA GAA GAC AGT GAC CCC GAG AAA GCA CTC AGA AAC GAG TAC TTT      2129
Glu Glu Glu Asp Ser Asp Pro Glu Lys Ala Leu Arg Asn Glu Tyr Phe
    505                 510                 515

GAA GCC GAG CCA GAG GAC CTG GTG GCG GGG ATC AAG ATC AAG CAC CTG      2177
Glu Ala Glu Pro Glu Asp Leu Val Ala Gly Ile Lys Ile Lys His Leu
520                 525                 530                 535

TCC AAG GTG TTC AGG GTG GGA AAT AAG GAC AGG GCG GCC GTC AGA GAC      2225
Ser Lys Val Phe Arg Val Gly Asn Lys Asp Arg Ala Ala Val Arg Asp
                540                 545                 550

CTG AAC CTC AAC CTG TAC GAG GGA CAG ATC ACC GTC CTG CTG GGC CAC      2273
Leu Asn Leu Asn Leu Tyr Glu Gly Gln Ile Thr Val Leu Leu Gly His
            555                 560                 565

AAC GGT GCC GGG AAG ACC ACC ACC CTC TCC ATG CTC ACA GGT CTC TTT      2321
Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Met Leu Thr Gly Leu Phe
        570                 575                 580

CCC CCC ACC AGT GGA CGG GCA TAC ATC AGC GGG TAT GAA ATT TCC CAG      2369
Pro Pro Thr Ser Gly Arg Ala Tyr Ile Ser Gly Tyr Glu Ile Ser Gln
    585                 590                 595

GAC ATG GTT CAG ATC CGG AAG AGC CTG GGC CTG TGC CCG CAG CAC GAC      2417
Asp Met Val Gln Ile Arg Lys Ser Leu Gly Leu Cys Pro Gln His Asp
600                 605                 610                 615

ATC CTG TTT GAC AAC TTG ACA GTC GCA GAG CAC CTT TAT TTC TAC GCC      2465
Ile Leu Phe Asp Asn Leu Thr Val Ala Glu His Leu Tyr Phe Tyr Ala
                620                 625                 630

CAG CTG AAG GGC CTG TCA CGT CAG AAG TGC CCT GAA GAA GTC AAG CAG      2513
Gln Leu Lys Gly Leu Ser Arg Gln Lys Cys Pro Glu Glu Val Lys Gln
            635                 640                 645

ATG CTG CAC ATC ATC GGC CTG GAG GAC AAG TGG AAC TCA CGG AGC CGC      2561
Met Leu His Ile Ile Gly Leu Glu Asp Lys Trp Asn Ser Arg Ser Arg
        650                 655                 660

TTC CTG AGC GGG GGC ATG AGG CGC AAG CTC TCC ATC GGC ATC GCC CTC      2609
Phe Leu Ser Gly Gly Met Arg Arg Lys Leu Ser Ile Gly Ile Ala Leu
    665                 670                 675

ATC GCA GGC TCC AAG GTG CTG ATA CTG GAC GAG CCC ACC TCG GGC ATG      2657
Ile Ala Gly Ser Lys Val Leu Ile Leu Asp Glu Pro Thr Ser Gly Met
680                 685                 690                 695

GAC GCC ATC TCC AGG AGG GCC ATC TGG GAT CTT CTT CAG CGG CAG AAA      2705
Asp Ala Ile Ser Arg Arg Ala Ile Trp Asp Leu Leu Gln Arg Gln Lys
                700                 705                 710

AGT GAC CGC ACC ATC GTG CTG ACC ACC CAC TTC ATG GAC GAG GCT GAC      2753
Ser Asp Arg Thr Ile Val Leu Thr Thr His Phe Met Asp Glu Ala Asp
            715                 720                 725

CTG CTG GGA GAC CGC ATC GCC ATC ATG GCC AAG GGG GAG CTG CAG TGC      2801
Leu Leu Gly Asp Arg Ile Ala Ile Met Ala Lys Gly Glu Leu Gln Cys
        730                 735                 740

TGC GGG TCC TCG CTG TTC CTC AAG CAG AAA TAC GGT GCC GGC TAT CAC      2849
Cys Gly Ser Ser Leu Phe Leu Lys Gln Lys Tyr Gly Ala Gly Tyr His
    745                 750                 755
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BNSDOCID: <WO___9748797A1_I_>

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ATG ACG CTG GTG AAG GAG CCG CAC TGC AAC CCG GAA GAC ATC TCC CAG      2897
Met Thr Leu Val Lys Glu Pro His Cys Asn Pro Glu Asp Ile Ser Gln
760                 765                 770                 775

CTG GTC CAC CAC CAC GTG CCC AAC GCC ACG CTG GAG AGC AGC GCT GGG      2945
Leu Val His His His Val Pro Asn Ala Thr Leu Glu Ser Ser Ala Gly
                780                 785                 790

GCC GAG CTG TCT TTC ATC CTT CCC AGA GAG AGC ACG CAC AGG TTT GAA      2993
Ala Glu Leu Ser Phe Ile Leu Pro Arg Glu Ser Thr His Arg Phe Glu
            795                 800                 805

GGT CTC TTT GCT AAA CTG GAG AAG AAG CAG AAA GAG CTG GGC ATT GCC      3041
Gly Leu Phe Ala Lys Leu Glu Lys Lys Gln Lys Glu Leu Gly Ile Ala
        810                 815                 820

AGC TTT GGG GCA TCC ATC ACC ACC ATG GAG GAA GTC TTC CTT CGG GTC      3089
Ser Phe Gly Ala Ser Ile Thr Thr Met Glu Glu Val Phe Leu Arg Val
    825                 830                 835

GGG AAG CTG GTG GAC AGC AGT ATG GAC ATC CAG GCC ATC CAG CTC CCT      3137
Gly Lys Leu Val Asp Ser Ser Met Asp Ile Gln Ala Ile Gln Leu Pro
840                 845                 850                 855

GCC CTG CAG TAC CAG CAC GAG AGG CGC GCC AGC GAC TGG GCT GTG GAC      3185
Ala Leu Gln Tyr Gln His Glu Arg Arg Ala Ser Asp Trp Ala Val Asp
                860                 865                 870

AGC AAC CTC TGT GGG GCC ATG GAC CCC TCC GAC GGC ATT GGA GCC CTC      3233
Ser Asn Leu Cys Gly Ala Met Asp Pro Ser Asp Gly Ile Gly Ala Leu
            875                 880                 885

ATC GAG GAG GAG CGC ACC GCT GTC AAG CTC AAC ACT GGG CTC GCC CTG      3281
Ile Glu Glu Glu Arg Thr Ala Val Lys Leu Asn Thr Gly Leu Ala Leu
        890                 895                 900

CAC TGC CAG CAA TTC TGG GCC ATG TTC CTG AAG AAG GCC GCA TAC AGC      3329
His Cys Gln Gln Phe Trp Ala Met Phe Leu Lys Lys Ala Ala Tyr Ser
    905                 910                 915

TGG CGC GAG TGG AAA ATG GTG GCG GCA CAG GTC CTG GTG CCT CTG ACC      3377
Trp Arg Glu Trp Lys Met Val Ala Ala Gln Val Leu Val Pro Leu Thr
920                 925                 930                 935

TGC GTC ACC CTG GCC CTC CTG GCC ATC AAC TAC TCC TCG GAG CTC TTC      3425
Cys Val Thr Leu Ala Leu Leu Ala Ile Asn Tyr Ser Ser Glu Leu Phe
                940                 945                 950

GAC GAC CCC ATG CTG AGG CTG ACC TTG GGC GAG TAC GGC AGA ACC GTC      3473
Asp Asp Pro Met Leu Arg Leu Thr Leu Gly Glu Tyr Gly Arg Thr Val
            955                 960                 965

GTG CCC TTC TCA GTT CCC GGG ACC TCC CAG CTG GGT CAG CAG CTG TCA      3521
Val Pro Phe Ser Val Pro Gly Thr Ser Gln Leu Gly Gln Gln Leu Ser
        970                 975                 980

GAG CAT CTG AAA GAC GCA CTG CAG GCT GAG GGA CAG GAG CCC CGC GAG      3569
Glu His Leu Lys Asp Ala Leu Gln Ala Glu Gly Gln Glu Pro Arg Glu
    985                 990                 995

GTG CTC GGT GAC CTG GAG GAG TTC TTG ATC TTC AGG GCT TCT GTG GAG      3617
Val Leu Gly Asp Leu Glu Glu Phe Leu Ile Phe Arg Ala Ser Val Glu
1000                1005                1010                1015
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BNSDOCID: <WO___9748797A1_I_>

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GGG GGC GGC TTT AAT GAG CGG TGC CTT GTG GCA GCG TCC TTC AGA GAT      3665
Gly Gly Gly Phe Asn Glu Arg Cys Leu Val Ala Ala Ser Phe Arg Asp
                1020                1025                1030

GTG GGA GAG CGC ACG GTC GTC AAC GCC TTG TTC AAC AAC CAG GCG TAC      3713
Val Gly Glu Arg Thr Val Val Asn Ala Leu Phe Asn Asn Gln Ala Tyr
            1035                1040                1045

CAC TCT CCA GCC ACT GCC CTG GCC GTC GTG GAC AAC CTT CTG TTC AAG      3761
His Ser Pro Ala Thr Ala Leu Ala Val Val Asp Asn Leu Leu Phe Lys
        1050                1055                1060

CTG CTG TGC GGG CCT CAC GCC TCC ATT GTG GTC TCC AAC TTC CCC CAG      3809
Leu Leu Cys Gly Pro His Ala Ser Ile Val Val Ser Asn Phe Pro Gln
    1065                1070                1075

CCC CGG AGC GCC CTG CAG GCT GCC AAG GAC CAG TTT AAC GAG GGC CGG      3857
Pro Arg Ser Ala Leu Gln Ala Ala Lys Asp Gln Phe Asn Glu Gly Arg
1080                1085                1090                1095

AAG GGA TTC GAC ATT GCC CTC AAC CTG CTC TTC GCC ATG GCA TTC TTG      3905
Lys Gly Phe Asp Ile Ala Leu Asn Leu Leu Phe Ala Met Ala Phe Leu
                1100                1105                1110

GCC AGC ACG TTC TCC ATC CTG GCG GTC AGC GAG AGG GCC GTG CAG GCC      3953
Ala Ser Thr Phe Ser Ile Leu Ala Val Ser Glu Arg Ala Val Gln Ala
            1115                1120                1125

AAG CAT GTG CAG TTT GTG AGT GGA GTC CAC GTG GCC AGT TTC TGG CTC      4001
Lys His Val Gln Phe Val Ser Gly Val His Val Ala Ser Phe Trp Leu
        1130                1135                1140

TCT GCT CTG CTG TGG GAC CTC ATC TCC TTC CTC ATC CCC AGT CTG CTG      4049
Ser Ala Leu Leu Trp Asp Leu Ile Ser Phe Leu Ile Pro Ser Leu Leu
    1145                1150                1155

CTG CTG GTG GTG TTT AAG GCC TTC GAC GTG CGT GCC TTC ACG CGG GAC      4097
Leu Leu Val Val Phe Lys Ala Phe Asp Val Arg Ala Phe Thr Arg Asp
1160                1165                1170                1175

GGC CAC ATG GCT GAC ACC CTG CTG CTG CTC CTG CTC TAC GGC TGG GCC      4145
Gly His Met Ala Asp Thr Leu Leu Leu Leu Leu Leu Tyr Gly Trp Ala
                1180                1185                1190

ATC ATC CCC CTC ATG TAC CTG ATG AAC TTC TTC TTC TTG GGG GCG GCC      4193
Ile Ile Pro Leu Met Tyr Leu Met Asn Phe Phe Phe Leu Gly Ala Ala
            1195                1200                1205

ACT GCC TAC ACG AGG CTG ACC ATC TTC AAC ATC CTG TCA GGC ATC GCC      4241
Thr Ala Tyr Thr Arg Leu Thr Ile Phe Asn Ile Leu Ser Gly Ile Ala
        1210                1215                1220

ACC TTC CTG ATG GTC ACC ATC ATG CGC ATC CCA GCT GTA AAA CTG GAA      4289
Thr Phe Leu Met Val Thr Ile Met Arg Ile Pro Ala Val Lys Leu Glu
    1225                1230                1235

GAA CTT TCC AAA ACC CTG GAT CAC GTG TTC CTG GTG CTG CCC AAC CAC      4337
Glu Leu Ser Lys Thr Leu Asp His Val Phe Leu Val Leu Pro Asn His
1240                1245                1250                1255

TGT CTG GGG ATG GCA GTC AGC AGT TTC TAC GAG AAC TAC GAG ACG CGG      4385
Cys Leu Gly Met Ala Val Ser Ser Phe Tyr Glu Asn Tyr Glu Thr Arg
                1260                1265                1270
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AGG TAC TGC ACC TCC TCC GAG GTC GCC GCC CAC TAC TGC AAG AAA TAT      4433
Arg Tyr Cys Thr Ser Ser Glu Val Ala Ala His Tyr Cys Lys Lys Tyr
            1275                1280                1285

AAC ATC CAG TAC CAG GAG AAC TTC TAT GCC TGG AGC GCC CCG GGG GTC      4481
Asn Ile Gln Tyr Gln Glu Asn Phe Tyr Ala Trp Ser Ala Pro Gly Val
        1290                1295                1300

GGC CGG TTT GTG GCC TCC ATG GCC GCC TCA GGG TGC GCC TAC CTC ATC      4529
Gly Arg Phe Val Ala Ser Met Ala Ala Ser Gly Cys Ala Tyr Leu Ile
    1305                1310                1315

CTG CTC TTC CTC ATC GAG ACC AAC CTG CTT CAG AGA CTC AGG GGC ATC      4577
Leu Leu Phe Leu Ile Glu Thr Asn Leu Leu Gln Arg Leu Arg Gly Ile
1320                1325                1330                1335

CTC TGC GCC CTC CGG AGG AGG CGG ACA CTG ACA GAA TTA TAC ACC CGG      4625
Leu Cys Ala Leu Arg Arg Arg Arg Thr Leu Thr Glu Leu Tyr Thr Arg
                1340                1345                1350

ATG CCT GTG CTT CCT GAG GAC CAA GAT GTA GCG GAC GAG AGG ACC CGC      4673
Met Pro Val Leu Pro Glu Asp Gln Asp Val Ala Asp Glu Arg Thr Arg
            1355                1360                1365

ATC CTG GCC CCC AGC CCG GAC TCC CTG CTC CAC ACA CCT CTG ATT ATC      4721
Ile Leu Ala Pro Ser Pro Asp Ser Leu Leu His Thr Pro Leu Ile Ile
        1370                1375                1380

AAG GAG CTC TCC AAG GTG TAC GAG CAG CGG GTG CCC CTC CTG GCC GTG      4769
Lys Glu Leu Ser Lys Val Tyr Glu Gln Arg Val Pro Leu Leu Ala Val
    1385                1390                1395

GAC AGG CTC TCC CTC GCG GTG CAG AAA GGG GAG TGC TTC GGC CTG CTG      4817
Asp Arg Leu Ser Leu Ala Val Gln Lys Gly Glu Cys Phe Gly Leu Leu
1400                1405                1410                1415

GGC TTC AAT GGA GCC GGG AAG ACC ACG ACT TTC AAA ATG CTG ACC GGG      4865
Gly Phe Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys Met Leu Thr Gly
                1420                1425                1430

GAG GAG AGC CTC ACT TCT GGG GAT GCC TTT GTC GGG GGT CAC AGA ATC      4913
Glu Glu Ser Leu Thr Ser Gly Asp Ala Phe Val Gly Gly His Arg Ile
            1435                1440                1445

AGC TCT GAT GTC GGA AAG GTG CGG CAG CGG ATC GGC TAC TGC CCG CAG      4961
Ser Ser Asp Val Gly Lys Val Arg Gln Arg Ile Gly Tyr Cys Pro Gln
        1450                1455                1460

TTT GAT GCC TTG CTG GAC CAC ATG ACA GGC CGG GAG ATG CTG GTC ATG      5009
Phe Asp Ala Leu Leu Asp His Met Thr Gly Arg Glu Met Leu Val Met
    1465                1470                1475

TAC GCT CGG CTC CGG GGC ATC CCT GAG CGC CAC ATC GGG GCC TGC GTG      5057
Tyr Ala Arg Leu Arg Gly Ile Pro Glu Arg His Ile Gly Ala Cys Val
1480                1485                1490                1495

GAG AAC ACT CTG CGG GGC CTG CTG CTG GAG CCA CAT GCC AAC AAG CTG      5105
Glu Asn Thr Leu Arg Gly Leu Leu Leu Glu Pro His Ala Asn Lys Leu
                1500                1505                1510

GTC AGG ACG TAC AGT GGT GGT AAC AAG CGG AAG CTG AGC ACC GGC ATC      5153
Val Arg Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser Thr Gly Ile
            1515                1520                1525
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GCC CTG ATC GGA GAG CCT GCT GTC ATC TTC CTG GAC GAG CCG TCC ACT      5201
Ala Leu Ile Gly Glu Pro Ala Val Ile Phe Leu Asp Glu Pro Ser Thr
        1530                1535                1540

GGC ATG GAC CCC GTG GCC CGG CGC CTG CTT TGG GAC ACC GTG GCA CGA      5249
Gly Met Asp Pro Val Ala Arg Arg Leu Leu Trp Asp Thr Val Ala Arg
    1545                1550                1555

GCC CGA GAG TCT GGC AAG GCC ATC ATC ATC ACC TCC CAC AGC ATG GAG      5297
Ala Arg Glu Ser Gly Lys Ala Ile Ile Ile Thr Ser His Ser Met Glu
1560                1565                1570                1575

GAG TGT GAG GCC CTG TGC ACC CGG CTG GCC ATC ATG GTG CAG GGG CAG      5345
Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val Gln Gly Gln
                1580                1585                1590

TTC AAG TGC CTG GGC AGC CCC CAG CAC CTC AAG AGC AAG TTC GGC AGC      5393
Phe Lys Cys Leu Gly Ser Pro Gln His Leu Lys Ser Lys Phe Gly Ser
            1595                1600                1605

GGC TAC TCC CTG CGG GCC AAG GTG CAG AGT GAA GGG CAA CAG GAG GCG      5441
Gly Tyr Ser Leu Arg Ala Lys Val Gln Ser Glu Gly Gln Gln Glu Ala
        1610                1615                1620

CTG GAG GAG TTC AAG GCC TTC GTG GAC CTG ACC TTT CCA GGC AGC GTC      5489
Leu Glu Glu Phe Lys Ala Phe Val Asp Leu Thr Phe Pro Gly Ser Val
    1625                1630                1635

CTG GAA GAT GAG CAC CAA GGC ATG GTC CAT TAC CAC CTG CCG GGC CGT      5537
Leu Glu Asp Glu His Gln Gly Met Val His Tyr His Leu Pro Gly Arg
1640                1645                1650                1655

GAC CTC AGC TGG GCG AAG GTT TTC GGT ATT CTG GAG AAA GCC AAG GAA      5585
Asp Leu Ser Trp Ala Lys Val Phe Gly Ile Leu Glu Lys Ala Lys Glu
                1660                1665                1670

AAG TAC GGC GTG GAC GAC TAC TCC GTG AGC CAG ATC TCG CTG GAA CAG      5633
Lys Tyr Gly Val Asp Asp Tyr Ser Val Ser Gln Ile Ser Leu Glu Gln
            1675                1680                1685

GTC TTC CTG AGC TTC GCC CAC CTG CAG CCG CCC ACC GCA GAG GAG GGG      5681
Val Phe Leu Ser Phe Ala His Leu Gln Pro Pro Thr Ala Glu Glu Gly
        1690                1695                1700

CGA TGAGGGGTGG CGGCTGTCTC GCCATCAGGC AGGGACAGGA CGGGCAAGCA           5734
Arg

GGGCCCATCT TACATCCTCT CTCTCCAAGT TTATCTCATC CTTTATTTTT AATCACTTTT    5794

TTCTATGATG GATATGAAAA ATTCAAGGCA GTATGCACAG AATGGACGAG TGCAGCCCAG    5854

CCCTCATGCC CAGGATCAGC ATGCGCATCT CCATGTCTGC ATACTCTGGA GTTCACTTTC    5914

CCAGAGCTGG GGCAGGCCGG GCAGTCTGCG GGCAAGCTCC GGGGTCTCTG GGTGGAGAGC    5974

TGACCCAGGA AGGGCTGCAG CTGAGCTGGG GGTTGAATTT CTCCAGGCAC TCCCTGGAGA    6034

GAGGACCCAG TGACTTGTCC AAGTTTACAC ACGACACTAA TCTCCCCTGG GGAGGAAGCG    6094

GGAAGCCAGC CAGGTTGAAC TGTAGCGAGG CCCCCAGGCC GCCAGGAATG GACCATGCAG    6154

ATCACTGTCA GTGGAGGGAA GCTGCTGACT GTGATTAGGT GCTGGGGTCT TAGCGTCCAG    6214

CGCAGCCCGG GGGCATCCTG GAGGCTCTGC TCCTTAGGGC ATGGTAGTCA CCGCGAAGCC    6274
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BNSDOCID: <WO___9748797A1_I_>

GGGCACCGTC CCACAGCATC TCCTAGAAGC AGCCGGCACA GGAGGGAAGG TGGCCAGGCT 6334

CGAAGCAGTC TCTGTTTCCA GCACTGCACC CTCAGGAAGT CGCCCCGCCC AGGACACGCA 6394

GGGACCACCC TAAGGGCTGG GTGGCTGTCT CAAGGACACA TTGAATACGT TGTGACCATC 6454

CAGAAAATAA ATGCTGAGGG GACACAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 6514

AAAAAAAAAA A 6525

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1704 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Met Ala Val Leu Arg Gln Leu Ala Leu Leu Leu Trp Lys Asn Tyr Thr
1 5 10 15

Leu Gln Lys Arg Lys Val Leu Val Thr Val Leu Glu Leu Phe Leu Pro
20 25 30

Leu Leu Phe Ser Gly Ile Leu Ile Trp Leu Arg Leu Lys Ile Gln Ser
35 40 45

Glu Asn Val Pro Asn Ala Thr Ile Tyr Pro Gly Gln Ser Ile Gln Glu
50 55 60

Leu Pro Leu Phe Phe Thr Phe Pro Pro Pro Gly Asp Thr Trp Glu Leu
65 70 75 80

Ala Tyr Ile Pro Ser His Ser Asp Ala Ala Lys Ala Val Thr Glu Thr
85 90 95

Val Arg Arg Ala Leu Val Ile Asn Met Arg Val Arg Gly Phe Pro Ser
100 105 110

Glu Lys Asp Phe Glu Asp Tyr Ile Arg Tyr Asp Asn Cys Ser Ser Ser
115 120 125

Val Leu Ala Ala Val Val Phe Glu His Pro Phe Asn His Ser Lys Glu
130 135 140

Pro Leu Pro Leu Ala Val Lys Tyr His Leu Arg Phe Ser Tyr Thr Arg
145 150 155 160

Arg Asn Tyr Met Trp Thr Gln Thr Gly Ser Phe Phe Leu Lys Glu Thr
165 170 175

Glu Gly Trp His Thr Thr Ser Leu Phe Pro Leu Phe Pro Asn Pro Gly
180 185 190

Pro Arg Glu Leu Thr Ser Pro Asp Gly Gly Glu Pro Gly Tyr Ile Arg
195 200 205

Glu Gly Phe Leu Ala Val Gln His Ala Val Asp Arg Ala Ile Met Glu
210 215 220

Tyr His Ala Asp Ala Ala Thr Arg Gln Leu Phe Gln Arg Leu Thr Val
225 230 235 240

BNSDOCID: <WO___9748797A1_I_>

Thr Ile Lys Arg Phe Pro Tyr Pro Pro Phe Ile Ala Asp Pro Phe Leu
245 250 255

Val Ala Ile Gln Tyr Gln Leu Pro Leu Leu Leu Leu Leu Ser Phe Thr
260 265 270

Tyr Thr Ala Leu Thr Ile Ala Arg Ala Val Val Gln Glu Lys Glu Arg
275 280 285

Arg Leu Lys Glu Tyr Met Arg Met Met Gly Leu Ser Ser Trp Leu His
290 295 300

Trp Ser Ala Trp Phe Leu Leu Phe Phe Leu Phe Leu Leu Ile Ala Ala
305 310 315 320

Ser Phe Met Thr Leu Leu Phe Cys Val Lys Val Lys Pro Asn Val Ala
325 330 335

Val Leu Ser Arg Ser Asp Pro Ser Leu Val Leu Ala Phe Leu Leu Cys
340 345 350

Phe Ala Ile Ser Thr Ile Ser Phe Ser Phe Met Val Ser Thr Phe Phe
355 360 365

Ser Lys Ala Asn Met Ala Ala Ala Phe Gly Gly Phe Leu Tyr Phe Phe
370 375 380

Thr Tyr Ile Pro Tyr Phe Phe Val Ala Pro Arg Tyr Asn Trp Met Thr
385 390 395 400

Leu Ser Gln Lys Leu Cys Ser Cys Leu Leu Ser Asn Val Ala Met Ala
405 410 415

Met Gly Ala Gln Leu Ile Gly Lys Phe Glu Ala Lys Gly Met Gly Ile
420 425 430

Gln Trp Arg Asp Leu Leu Ser Pro Val Asn Val Asp Asp Asp Phe Cys
435 440 445

Phe Gly Gln Val Leu Gly Met Leu Leu Leu Asp Ser Val Leu Tyr Gly
450 455 460

Leu Val Thr Trp Tyr Met Glu Ala Val Phe Pro Gly Gln Phe Gly Val
465 470 475 480

Pro Gln Pro Trp Tyr Phe Phe Ile Met Pro Ser Tyr Trp Cys Gly Lys
485 490 495

Pro Arg Ala Val Ala Gly Lys Glu Glu Glu Asp Ser Asp Pro Glu Lys
500 505 510

Ala Leu Arg Asn Glu Tyr Phe Glu Ala Glu Pro Glu Asp Leu Val Ala
515 520 525

Gly Ile Lys Ile Lys His Leu Ser Lys Val Phe Arg Val Gly Asn Lys
530 535 540

Asp Arg Ala Ala Val Arg Asp Leu Asn Leu Asn Leu Tyr Glu Gly Gln
545 550 555 560

Ile Thr Val Leu Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu
565 570 575

Ser Met Leu Thr Gly Leu Phe Pro Pro Thr Ser Gly Arg Ala Tyr Ile
580 585 590

BNSDOCID: <WO___9748797A1_I_>

Ser Gly Tyr Glu Ile Ser Gln Asp Met Val Gln Ile Arg Lys Ser Leu
595 600 605

Gly Leu Cys Pro Gln His Asp Ile Leu Phe Asp Asn Leu Thr Val Ala
610 615 620

Glu His Leu Tyr Phe Tyr Ala Gln Leu Lys Gly Leu Ser Arg Gln Lys
625 630 635 640

Cys Pro Glu Glu Val Lys Gln Met Leu His Ile Ile Gly Leu Glu Asp
645 650 655

Lys Trp Asn Ser Arg Ser Arg Phe Leu Ser Gly Gly Met Arg Arg Lys
660 665 670

Leu Ser Ile Gly Ile Ala Leu Ile Ala Gly Ser Lys Val Leu Ile Leu
675 680 685

Asp Glu Pro Thr Ser Gly Met Asp Ala Ile Ser Arg Arg Ala Ile Trp
690 695 700

Asp Leu Leu Gln Arg Gln Lys Ser Asp Arg Thr Ile Val Leu Thr Thr
705 710 715 720

His Phe Met Asp Glu Ala Asp Leu Leu Gly Asp Arg Ile Ala Ile Met
725 730 735

Ala Lys Gly Glu Leu Gln Cys Cys Gly Ser Ser Leu Phe Leu Lys Gln
740 745 750

Lys Tyr Gly Ala Gly Tyr His Met Thr Leu Val Lys Glu Pro His Cys
755 760 765

Asn Pro Glu Asp Ile Ser Gln Leu Val His His His Val Pro Asn Ala
770 775 780

Thr Leu Glu Ser Ser Ala Gly Ala Glu Leu Ser Phe Ile Leu Pro Arg
785 790 795 800

Glu Ser Thr His Arg Phe Glu Gly Leu Phe Ala Lys Leu Glu Lys Lys
805 810 815

Gln Lys Glu Leu Gly Ile Ala Ser Phe Gly Ala Ser Ile Thr Thr Met
820 825 830

Glu Glu Val Phe Leu Arg Val Gly Lys Leu Val Asp Ser Ser Met Asp
835 840 845

Ile Gln Ala Ile Gln Leu Pro Ala Leu Gln Tyr Gln His Glu Arg Arg
850 855 860

Ala Ser Asp Trp Ala Val Asp Ser Asn Leu Cys Gly Ala Met Asp Pro
865 870 875 880

Ser Asp Gly Ile Gly Ala Leu Ile Glu Glu Glu Arg Thr Ala Val Lys
885 890 895

Leu Asn Thr Gly Leu Ala Leu His Cys Gln Gln Phe Trp Ala Met Phe
900 905 910

Leu Lys Lys Ala Ala Tyr Ser Trp Arg Glu Trp Lys Met Val Ala Ala
915 920 925

Gln Val Leu Val Pro Leu Thr Cys Val Thr Leu Ala Leu Leu Ala Ile
930 935 940

BNSDOCID: <WO___9748797A1_I_>

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Gly Glu Tyr Gly Arg Thr Val Val Pro Phe Ser Val Pro Gly Thr Ser
965 970 975

Gln Leu Gly Gln Gln Leu Ser Glu His Leu Lys Asp Ala Leu Gln Ala
980 985 990

Glu Gly Gln Glu Pro Arg Glu Val Leu Gly Asp Leu Glu Glu Phe Leu
995 1000 1005

Ile Phe Arg Ala Ser Val Glu Gly Gly Gly Phe Asn Glu Arg Cys Leu
1010 1015 1020

Val Ala Ala Ser Phe Arg Asp Val Gly Glu Arg Thr Val Val Asn Ala
1025 1030 1035 1040

Leu Phe Asn Asn Gln Ala Tyr His Ser Pro Ala Thr Ala Leu Ala Val
1045 1050 1055

Val Asp Asn Leu Leu Phe Lys Leu Leu Cys Gly Pro His Ala Ser Ile
1060 1065 1070

Val Val Ser Asn Phe Pro Gln Pro Arg Ser Ala Leu Gln Ala Ala Lys
1075 1080 1085

Asp Gln Phe Asn Glu Gly Arg Lys Gly Phe Asp Ile Ala Leu Asn Leu
1090 1095 1100

Leu Phe Ala Met Ala Phe Leu Ala Ser Thr Phe Ser Ile Leu Ala Val
1105 1110 1115 1120

Ser Glu Arg Ala Val Gln Ala Lys His Val Gln Phe Val Ser Gly Val
1125 1130 1135

His Val Ala Ser Phe Trp Leu Ser Ala Leu Leu Trp Asp Leu Ile Ser
1140 1145 1150

Phe Leu Ile Pro Ser Leu Leu Leu Leu Val Val Phe Lys Ala Phe Asp
1155 1160 1165

Val Arg Ala Phe Thr Arg Asp Gly His Met Ala Asp Thr Leu Leu Leu
1170 1175 1180

Leu Leu Leu Tyr Gly Trp Ala Ile Ile Pro Leu Met Tyr Leu Met Asn
1185 1190 1195 1200

Phe Phe Phe Leu Gly Ala Ala Thr Ala Tyr Thr Arg Leu Thr Ile Phe
1205 1210 1215

Asn Ile Leu Ser Gly Ile Ala Thr Phe Leu Met Val Thr Ile Met Arg
1220 1225 1230

Ile Pro Ala Val Lys Leu Glu Glu Leu Ser Lys Thr Leu Asp His Val
1235 1240 1245

Phe Leu Val Leu Pro Asn His Cys Leu Gly Met Ala Val Ser Ser Phe
1250 1255 1260

Tyr Glu Asn Tyr Glu Thr Arg Arg Tyr Cys Thr Ser Ser Glu Val Ala
1265 1270 1275 1280

Ala His Tyr Cys Lys Lys Tyr Asn Ile Gln Tyr Gln Glu Asn Phe Tyr
1285 1290 1295

BNSDOCID: <WO___9748797A1_I_>

Ala Trp Ser Ala Pro Gly Val Gly Arg Phe Val Ala Ser Met Ala Ala
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Ser Gly Cys Ala Tyr Leu Ile Leu Leu Phe Leu Ile Glu Thr Asn Leu
1315 1320 1325

Leu Gln Arg Leu Arg Gly Ile Leu Cys Ala Leu Arg Arg Arg Arg Thr
1330 1335 1340

Leu Thr Glu Leu Tyr Thr Arg Met Pro Val Leu Pro Glu Asp Gln Asp
1345 1350 1355 1360

Val Ala Asp Glu Arg Thr Arg Ile Leu Ala Pro Ser Pro Asp Ser Leu
1365 1370 1375

Leu His Thr Pro Leu Ile Ile Lys Glu Leu Ser Lys Val Tyr Glu Gln
1380 1385 1390

Arg Val Pro Leu Leu Ala Val Asp Arg Leu Ser Leu Ala Val Gln Lys
1395 1400 1405

Gly Glu Cys Phe Gly Leu Leu Gly Phe Asn Gly Ala Gly Lys Thr Thr
1410 1415 1420

Thr Phe Lys Met Leu Thr Gly Glu Glu Ser Leu Thr Ser Gly Asp Ala
1425 1430 1435 1440

Phe Val Gly Gly His Arg Ile Ser Ser Asp Val Gly Lys Val Arg Gln
1445 1450 1455

Arg Ile Gly Tyr Cys Pro Gln Phe Asp Ala Leu Leu Asp His Met Thr
1460 1465 1470

Gly Arg Glu Met Leu Val Met Tyr Ala Arg Leu Arg Gly Ile Pro Glu
1475 1480 1485

Arg His Ile Gly Ala Cys Val Glu Asn Thr Leu Arg Gly Leu Leu Leu
1490 1495 1500

Glu Pro His Ala Asn Lys Leu Val Arg Thr Tyr Ser Gly Gly Asn Lys
1505 1510 1515 1520

Arg Lys Leu Ser Thr Gly Ile Ala Leu Ile Gly Glu Pro Ala Val Ile
1525 1530 1535

Phe Leu Asp Glu Pro Ser Thr Gly Met Asp Pro Val Ala Arg Arg Leu
1540 1545 1550

Leu Trp Asp Thr Val Ala Arg Ala Arg Glu Ser Gly Lys Ala Ile Ile
1555 1560 1565

Ile Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu
1570 1575 1580

Ala Ile Met Val Gln Gly Gln Phe Lys Cys Leu Gly Ser Pro Gln His
1585 1590 1595 1600

Leu Lys Ser Lys Phe Gly Ser Gly Tyr Ser Leu Arg Ala Lys Val Gln
1605 1610 1615

Ser Glu Gly Gln Gln Glu Ala Leu Glu Glu Phe Lys Ala Phe Val Asp
1620 1625 1630

Leu Thr Phe Pro Gly Ser Val Leu Glu Asp Glu His Gln Gly Met Val
1635 1640 1645

BNSDOCID: <WO___9748797A1_I_>

His Tyr His Leu Pro Gly Arg Asp Leu Ser Trp Ala Lys Val Phe Gly
1650 1655 1660

Ile Leu Glu Lys Ala Lys Glu Lys Tyr Gly Val Asp Asp Tyr Ser Val
1665 1670 1675 1680

Ser Gln Ile Ser Leu Glu Gln Val Phe Leu Ser Phe Ala His Leu Gln
1685 1690 1695

Pro Pro Thr Ala Glu Glu Gly Arg
1700

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Oligonucleotide primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

AGCTGGCGCT CCTCCTCT 18

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 349 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Gly Gln Leu Leu Gly His Asn Gly Ala Gly Lys Thr Thr Ser Ile Gly
1 5 10 15

Arg Pro Thr Gly Ile Gly Tyr Asp Arg Gly Cys Pro Gln Leu Asp Leu
20 25 30

Thr Val Glu His Leu Leu Lys Gly Lys Leu Leu Lys Asn Leu Ser Gly
35 40 45

Gly Met Arg Lys Leu Gly Leu Asp Glu Pro Thr Ala Gly Met Asp Arg
50 55 60

Leu Arg Lys Arg Thr Ile Leu Thr Thr His Met Asp Glu Ala Leu Gly
65 70 75 80

Asp Ile Met His Gly Leu Gly Leu Lys Gln Lys Gly Gly Tyr Thr Val
85 90 95

Glu Gln Pro Ala Arg Phe Leu Leu Ser Phe Gly Ser Thr Glu Val Phe
100 105 110

BNSDOCID: <WO___9748797A1_I_>

Ile Gly Asp His Arg Gly Ala Gln Phe Lys Lys Tyr Ser Arg Trp Gln
115 120 125

Val Leu Pro Leu Asp Leu Thr Glu Val Phe Pro Leu Pro Gly Ala Leu
130 135 140

Phe Asn Tyr His Thr Ser Val Ser Gln Ala Leu Ala Ser Thr Phe Glu
145 150 155 160

Arg Gln Ala His Gln Phe Gly Phe Leu Asp Ile Ser Leu Leu Phe Asp
165 170 175

His Ala Leu Leu Tyr Ser Pro Tyr Phe Phe Ala Leu Ile Ala Leu Val
180 185 190

Glu Leu Leu Phe Leu Pro Gly Ala Asn Trp Gly Phe Leu Arg Met Leu
195 200 205

Pro Val Glu Arg Arg Asn Leu Ile Lys Leu Lys Ala Val Leu Leu Ala
210 215 220

Val Glu Cys Phe Gly Leu Leu Gly Asn Gly Ala Gly Lys Thr Thr Thr
225 230 235 240

Phe Leu Thr Gly Ser Ser Gly Ala Gly Gly Asp Val Ile Gly Tyr Cys
245 250 255

Pro Gln Phe Asp Ala Leu Thr Gly Arg Glu Leu Ala Gly Ala Glu Leu
260 265 270

His Ala Lys Leu Val Arg Tyr Ser Gly Gly Lys Arg Lys Ser Gly Ala
275 280 285

Leu Leu Pro Gln Ile Leu Asp Glu Pro Gly Asp Pro Ala Arg Arg Trp
290 295 300

Glu Ser Ala Thr Ser His Ser Met Glu Cys Glu Ala Leu Cys Arg Ala
305 310 315 320

Gly Gly Ser Gln Leu Lys Ser Gly Tyr Val Pro Ser Val Leu Leu Pro
325 330 335

Trp Phe Gly Val Asp Gln Ser Leu Glu Phe Leu Ala Leu
340 345

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1974 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

CAGCGGGAGG ACGCGCCAAC ATCCCCGCTG CTGTGCTGGG CCCGGGGCGT GCCCGCCGCT 60

GCTCCCACCT CTGGGCCGGG CTGGGGCCGC CCGGGGGCCC TGTTCCTCGG CATTGCGGGC 120

CTGGTGGGCA GAACCGCGGA GAGGGCTTCT TTTCCCCAAG GGCAGCGTCT TGGGGCCCGG 180

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CCACTGGCTG ACCCGCAGCG GCTCCGGCCA TGCCTGGCTG GCCCTGGGGG CTGCTGCTGA 240

CGGCAGGCAC GCTCTTCGCC GCCCTGAGTC CTGGGCCGCC GGCGCCCGCC GACCCCTGCC 300

ACGATGAGGG GGGTGCGCCC CGCGGCTGCG TGCCAGGACT GGTGAACGCC GCCCTGGGCC 360

GCGAGGTGCT GGCTTCCAGC ACGTGCGGGC GGCCGGCCAC TCGGGCCTGC GACGCCTCCG 420

ACCCCGCGACG GGCACACTCC CCCGCCCTCC TTACTTCCCC AGGGGGCACG GCCAGCCCTC 480

TGTGCTGGCG CTCGGAGTCC CTGCCTCGGG CGCCCCTCAA CGTGACTCTC ACGGTGCCCC 540

TGGGCAAGGC TTTTGAGCTG GTCTTCGTGA GCCTGCGCTT CTGCTCAGCT CCCCCAGCCT 600

CCGTGGCCCT GCTCAAGTCT CAGGACCATG GCCGCAGCTG GGCCCCGCTG GGCTTCTTCT 660

CCTCCCACTG TGACCTGGAC TATGGCCGTC TGCCTGCCCC TGCCAATGGC CCAGCTGGCC 720

CAGGGCCTGA GGCCCTGTGC TTCCCCGCAC CCCTGGCCCA GCCTGATGGC AGCGGCCTTC 780

TGGCCTTCAG CATGCAGGAC AGCAGCCCCC CAGGCCTGGA CCTGGACAGC AGCCCAGTGC 840

TCCAAGACTG GGTGACCGCC ACCGACGTCC GTGTAGTGCT CACAAGGCCT AGCACGGCAG 900

GTGACCCCAG GGACATGGAG GCCGTCGTCC CTTACTCCTA CGCAGCCACC GACCTCCAGG 960

TGGGCGGGCG CTGCAAGTGC AATGGACATG CCTCACGGTG CCTGCTGGAC ACACAGGGCC 1020

ACCTGATCTG CGACTGTCGG CATGGCACCG AGGGCCCTGA CTGCGGCCGC TGCAAGCCCT 1080

TCTACTGCGA CAGGCCATGG CAGCGGGCCA CTGCCCGGGA ATCCCACGCC TGCCTCGCTT 1140

GCTCCTGCAA CGGCCATGCC CGCCGCTGCC GCTTCAACAT GGAGCTGTAC CGACTGTCCG 1200

GCCGCCGCAG CGGGGGTGTC TGTCTCAACT GCCGGCACAA CACCGCCGGC CGCCACTGCC 1260

ACTACTGCCG GGAGGGCTTC TATCGAGACC CTGGCCGTGC CCTGAGTGAC CGTCGGGCTT 1320

GCAGGGCCTG CGACTGTCAC CCGGTTGGTG CTGCTGGCAA GACCTGCAAC CAGACCACAG 1380

GCCAGTGTCC CTGCAAGGAT GGCGTCACTG GCCTCACCTG CAACCGCTGC GCGCCTGGCT 1440

TCCAGCAAAG CCGCTCCCCA GTGGCGCCCT GTGTTAAGAC CCCTATCCCT GGACCCACTG 1500

AGGACAGCAG CCCTGTGCAG CCCCAGGACT GTGACTCGCA CTGCAAACCT GCCCGTGGCA 1560

GCTACCGCAT CAGCCTAAAG AAGTTCTGCA AGAAGGACTA TGCCGTGCAG GTGGCGGTGG 1620

GTGCGCGCGG CGAGGCGCGC GGCGCGTGGA CACGCTTCCC GGTGGCGGTG CTCGCCGTGT 1680

TCCGGAGCGG AGAGGAGCGC GCGCGGCGCG GGAGTAGCGC GCTGTGGGTG CCCGCCGGGG 1740

ATGCGGCCTG CGGCTGCCCG CGCCTGCTCC CCGGCCGCCG CTACCTCCTG CTGGGGGGCG 1800

GGCCTGGAGC CGCGGCTGGG GGCGCGGGGG GCCGGGGGCC CGGGCTCATC GCCGCCCGCG 1860

GAAGCCTCGT GCTACCCTGG AGGGACGCGT GGACGCGGCG CCTGCGGAGG CTGCAGCGAC 1920

GCGAACGGCG GGGGCGCTGC AGCGCCGCCT GAGCCCGCCG GCTGGGCAAG GCGC 1974

BNSDOCID: <WO___9748797A1_I_>

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 612 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Met Ile Thr Ser Val Leu Arg Tyr Val Leu Ala Leu Tyr Phe Cys Met
1 5 10 15

Gly Ile Ala His Gly Ala Tyr Phe Ser Gln Phe Ser Met Arg Ala Pro
20 25 30

Asp His Asp Pro Cys His Asp His Thr Gly Arg Pro Val Arg Cys Val
35 40 45

Pro Glu Phe Ile Asn Ala Ala Phe Gly Lys Pro Val Ile Ala Ser Asp
50 55 60

Thr Cys Gly Thr Asn Arg Pro Asp Lys Tyr Cys Thr Val Lys Glu Gly
65 70 75 80

Pro Asp Gly Ile Ile Arg Glu Gln Cys Asp Thr Cys Asp Ala Arg Asn
85 90 95

His Phe Gln Ser His Pro Ala Ser Leu Leu Thr Asp Leu Asn Ser Ile
100 105 110

Gly Asn Met Thr Cys Trp Val Ser Thr Pro Ser Leu Ser Pro Gln Asn
115 120 125

Val Ser Leu Thr Leu Ser Leu Gly Lys Lys Phe Glu Leu Thr Tyr Val
130 135 140

Ser Met His Phe Cys Ser Arg Leu Pro Asp Ser Met Ala Leu Tyr Lys
145 150 155 160

Ser Ala Asp Phe Gly Lys Thr Trp Thr Pro Phe Gln Phe Tyr Ser Ser
165 170 175

Glu Cys Arg Arg Ile Phe Gly Arg Asp Pro Asp Val Ser Ile Thr Lys
180 185 190

Ser Asn Glu Gln Glu Ala Val Cys Thr Ala Ser His Ile Met Gly Pro
195 200 205

Gly Gly Asn Arg Val Ala Phe Pro Phe Leu Glu Asn Arg Pro Ser Ala
210 215 220

Gln Asn Phe Glu Asn Ser Pro Val Leu Gln Asp Trp Val Thr Ala Thr
225 230 235 240

Asp Ile Lys Val Val Phe Ser Arg Leu Ser Pro Asp Gln Ala Glu Leu
245 250 255

Tyr Gly Leu Ser Asn Asp Val Asn Ser Tyr Gly Asn Glu Thr Asp Asp
260 265 270

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Glu Val Lys Gln Arg Tyr Phe Tyr Ser Met Gly Glu Leu Ala Val Gly
375 280 285

Gly Arg Cys Lys Cys Asn Gly His Ala Ser Arg Cys Ile Phe Asp Lys
290 295 300

Met Gly Arg Tyr Thr Cys Asp Cys Lys His Asn Thr Ala Gly Thr Glu
305 310 315 320

Cys Glu Met Cys Lys Pro Phe His Tyr Asp Arg Pro Trp Gly Arg Ala
325 330 335

Thr Ala Asn Ser Ala Asn Ser Cys Val Ala Cys Asn Cys Asn Gln His
340 345 350

Ala Lys Arg Cys Arg Phe Asp Ala Glu Leu Phe Arg Leu Ser Gly Asn
355 360 365

Arg Ser Gly Gly Val Cys Leu Asn Cys Arg His Asn Thr Ala Gly Arg
370 375 380

Asn Cys His Leu Cys Lys Pro Gly Phe Val Arg Asp Thr Ser Leu Pro
385 390 395 400

Met Thr His Arg Arg Ala Cys Lys Ser Cys Gly Cys His Pro Val Gly
405 410 415

Ser Leu Gly Lys Ser Cys Asn Gln Ser Ser Gly Gln Cys Val Cys Lys
420 425 430

Pro Gly Val Thr Gly Thr Thr Cys Asn Arg Cys Ala Lys Gly Tyr Gln
435 440 445

Gln Ser Arg Ser Thr Val Thr Pro Cys Ile Lys Ile Pro Thr Lys Ala
450 455 460

Asp Phe Ile Gly Ser Ser His Ser Glu Glu Gln Asp Gln Cys Ser Lys
465 470 475 480

Cys Arg Ile Val Pro Lys Arg Leu Asn Gln Lys Lys Phe Cys Lys Arg
485 490 495

Asp His Ala Val Gln Met Val Val Val Ser Arg Glu Met Val Asp Gly
500 505 510

Trp Ala Lys Tyr Lys Ile Val Val Glu Ser Val Phe Lys Arg Thr Glu
515 520 525

Asn Met Gln Arg Arg Gly Glu Thr Ser Leu Trp Ile Ser Pro Gln Gly
530 535 540

Val Ile Cys Lys Cys Pro Lys Leu Arg Val Gly Arg Arg Tyr Leu Leu
545 550 555 560

Leu Gly Lys Asn Asp Ser Asp His Glu Arg Asp Gly Leu Met Val Asn
565 570 575

Pro Gln Thr Val Leu Val Glu Trp Glu Asp Asp Ile Met Asp Lys Val
580 585 590

Leu Arg Phe Ser Lys Lys Asp Lys Leu Gly Gln Cys Pro Glu Ile Thr
595 600 605

Ser His Arg Tyr
610

BNSDOCID: <WO___9748797A1_I_>

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Oligonucleotide primer - sense strand"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

CTTGCAGGGC CTGCGAC 17

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Oligonucleotide primer - antisense strand"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

GAAGGCACAG GGTGAAC 17

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Oligonucleotide primer - sense strand"

BNSDOCID: <WO___9748797A1_I_>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

CTGCAACCAG ACCACAG 17

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "Oligonucleotide primer - antisense strand"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

TAGATGTGGG AGCAGCG 17

BNSDOCID: <WO___9748797A1_I_>

What is claimed is:

1. Isolated nucleic acid encoding human netrin (hNET) or its complement.

2. Isolated nucleic acid according to claim 1, wherein said nucleic acid is mRNA.

3. Isolated nucleic acid according to claim 1, wherein said nucleic acid is DNA comprising the sequence set forth in SEQ ID NO:19.

4. Isolated nucleic acid according to claim 1, wherein said nucleic acid is DNA comprising the sequence set forth in SEQ ID NO:20.

5. Isolated nucleic acid according to claim 1, wherein said nucleic acid is DNA comprising the sequence set forth in SEQ ID NO:78.

6. Isolated nucleic acid that hybridizes under stringent conditions to the nucleic acid of claim 1.

7. Isolated nucleic acid according to claim 6, comprising the sequence: 5'-GCCTGTCATCGCTCTAG-3' (SEQ ID NO:59).

8. Isolated nucleic acid according to claim 6, comprising the sequence: 5'-CAGTCGCAGGCCCTGCA-3' (SEQ ID NO:60).

9. Isolated nucleic acid according to claim 6, comprising the sequence: 5'-GAGGACGCGCCAACATC-3' (SEQ ID NO:61).

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10. Isolated nucleic acid according to claim 6, comprising the sequence: 5'-CGGCAGTAGTGGCAGTG-3' (SEQ ID NO:62).

11. Isolated nucleic acid according to claim 6, comprising the sequence: 5'-CCTGCCTCGCTTGCTCCTGC-3' (SEQ ID NO:63).

12. Isolated nucleic acid according to claim 6, comprising the sequence: 5'-CGGGCAGCCGCAGGCCGCAT-3' (SEQ ID NO:64).

13. Isolated nucleic acid according to claim 6, comprising the sequence: 5'-CCTGCAACGGCCATGCCCGC-3' (SEQ ID NO:65).

14. Isolated nucleic acid according to claim 6, comprising the sequence: 5'-GCATCCCCGGCGGGCACCCA-3' (SEQ ID NO:66).

15. Isolated nucleic acid according to claim 6, comprising the sequence: 5'-CTTGCAGGGCCTGCGAC-3' (SEQ ID NO:80).

16. Isolated nucleic acid according to claim 6, comprising the sequence 5'-GAAGGCACAGGGTGAAC-3' (SEQ ID NO:81).

17. Isolated nucleic acid according to claim 6, comprising the sequence 5'-CTGCAACCAGACCACAG-3' (SEQ ID NO:82).

18. Isolated nucleic acid according to claim 6, comprising the sequence 5'-TAGATGTGGGAGCAGCG-3' (SEQ ID NO:83).

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19. An antisense oligonucleotide that specifically binds to and modulates translation of mRNA according to claim 2.

20. Isolated human netrin (hNET) and biologically active fragments thereof.

21. Isolated hNET according to claim 20 comprising the amino acid sequence set forth in SEQ ID NO:21.

22. A vector comprising the isolated nucleic acid of claim 1.

23. A host cell comprising the vector of claim 22.

24. A method for producing human netrin protein, said method comprising:

(a) culturing the host cell of claim 23 in a medium and under conditions suitable for expression of said protein, and

(b) isolating said expressed protein.

25. An antibody that specifically binds to human netrin (hNET).

26. A composition comprising an amount of the oligonucleotide according to claim 19, effective to modulate expression of hNET by passing through a cell membrane and binding specifically with mRNA encoding hNET in the cell so as to prevent its translation and an acceptable hydrophobic carrier capable of passing through a cell membrane.

27. A composition comprising an amount of the antibody according to claim 25, effective to block binding

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of naturally occurring ligands to hNET and an acceptable carrier.

28. A transgenic non-human mammal expressing DNA encoding human netrin (hNET).

29. A method for identifying compounds which bind to human netrin (hNET), said method comprising a competitive binding assay wherein the cells according to claim 23 are exposed to a plurality of compounds and identifying compounds which bind thereto.

30. Isolated nucleic acid encoding human ATP Binding Cassette transporter (hABC3) or its complement.

31. Isolated nucleic acid according to claim 30, wherein said nucleic acid is mRNA.

32. Isolated nucleic acid according to claim 30, wherein said nucleic acid is DNA comprising the sequence set forth in SEQ ID NO:24.

33. Isolated nucleic acid according to claim 30, wherein said nucleic acid is DNA comprising the sequence set forth in SEQ ID NO:74.

34. Isolated nucleic acid that hybridizes under stringent conditions to the nucleic acid of claim 30.

35. Isolated nucleic acid according to claim 34, comprising the sequence: 5'-GACGCTGGTGAAGGAGC-3' (SEQ ID NO:42).

36. Isolated nucleic acid according to claim 34, comprising the sequence: 5'-TCGCTGACCGCCAGGAT-3' (SEQ ID NO:43).

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37. Isolated nucleic acid according to claim 34, comprising the sequence: 5'-CATTGCCCGTGCTGTCGTG-3' (SEQ ID NO:52).

38. Isolated nucleic acid according to claim 34, comprising the sequence: 5'-CATCGCCGCCTCCTTCATG-3' (SEQ ID NO:53).

39. Isolated nucleic acid according to claim 34, comprising the sequence: 5'-GCGGAGCCACCTTCATCA-3' (SEQ ID NO:54).

40. Isolated nucleic acid according to claim 34, comprising the sequence: 5'-GACGCTGGTGAAGGAGC-3' (SEQ ID NO:55).

41. Isolated nucleic acid according to claim 34, comprising the sequence: 5'-ATCCTGGCGGTCAGCGA-3' (SEQ ID NO:56).

42. Isolated nucleic acid according to claim 34, comprising the sequence: 5'-AGGGATTCGACATTGCC-3' (SEQ ID NO:57).

43. Isolated nucleic acid according to claim 34, comprising the sequence: 5'-CTTCAGAGACTCAGGGGCAT-3' (SEQ ID NO:58).

44. Isolated nucleic acid according to claim 34, comprising the sequence 5'-AGCTGGCGCTCCTCCTCT-3' (SEQ ID NO:76).

45. An antisense oligonucleotide that specifically binds to and modulates translation of mRNA according to claim 31.

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46. Isolated human ATP binding cassette transporter (hABC3) and biologically active fragments thereof.

47. Isolated hABC3 according to claim 46 comprising the amino acid sequence set forth in SEQ ID NO:25.

48. Isolated hABC3 according to claim 46 comprising the amino acid sequence set forth in SEQ ID NO:75.

49. A vector comprising the isolated nucleic acid of claim 30.

50. A host cell comprising the vector of claim 49.

51. A method for producing human ATP binding cassette transporter (hABC3), said method comprising:

(a) culturing the host cell of claim 50 in a medium and under conditions suitable for expression of said protein, and

(b) isolating said expressed protein.

52. An antibody that specifically binds to human ATP binding cassette transporter (hABC3).

53. A composition comprising an amount of the oligonucleotide according to claim 45, effective to modulate expression of hABC3 by passing through a cell membrane and binding specifically with mRNA encoding hABC3 in the cell so as to prevent its translation and an acceptable hydrophobic carrier capable of passing through a cell membrane.

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54. A composition comprising an amount of the antibody according to claim 52, effective to block binding of naturally occurring ligands to hABC3 and an acceptable carrier.

55. A transgenic non-human mammal expressing DNA encoding human ATP binding cassette transporter (hABC3).

56. A method for identifying compounds which bind to human ATP binding cassette transporter (hABC3), said method comprising a competitive binding assay wherein the cells according to claim 50 are exposed to a plurality of compounds and identifying compounds which bind thereto.

57. Isolated nucleic acid encoding human ribosomal L3 (RPL3L) or its complement.

58. Isolated nucleic acid according to claim 57, wherein said nucleic acid is mRNA.

59. Isolated nucleic acid according to claim 57, wherein said nucleic acid is DNA comprising the sequence set forth in SEQ ID NO:28.

60. Isolated nucleic acid that hybridizes under stringent conditions to the nucleic acid of claim 57.

61. Isolated nucleic acid according to claim 60, comprising the sequence: 5'-ACGGACACCTGGGCTTC-3' (SEQ ID NO:48).

62. Isolated nucleic acid according to claim 60, comprising the sequence: 5'-AAACGGGAGGAGGTGGA-3' (SEQ ID NO:49).

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63. Isolated nucleic acid according to claim 60, comprising the sequence: 5'-AGACAGCCCAAGAGAAGAGG-3' (SEQ ID NO:73).

64. An antisense oligonucleotide that specifically binds to and modulates translation of mRNA according to claim 58.

65. Isolated human ribosomal L3 (RPL3L) and biologically active fragments thereof.

66. Isolated RPL3L according to claim 65 comprising the amino acid sequence set forth in SEQ ID NO:29.

67. A vector comprising the isolated nucleic acid of claim 57.

68. A host cell comprising the vector of claim 67.

69. A method for producing human ribosomal L3 (RPL3L), said method comprising:

(a) culturing the host cell of claim 68 in a medium and under conditions suitable for expression of said protein, and

(b) isolating said expressed protein.

70. An antibody that specifically binds to human ribosomal L3 (RPL3L).

71. A composition comprising an amount of the oligonucleotide according to claim 64, effective to modulate expression of RPL3L by passing through a cell membrane and binding specifically with mRNA encoding RPL3L in the cell so as to prevent its translation and an

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acceptable hydrophobic carrier capable of passing through a cell membrane.

72. A composition comprising an amount of the antibody according to claim 70, effective to block binding of naturally occurring ligands to RPL3L and an acceptable carrier.

73. A transgenic non-human mammal expressing DNA encoding human ribosomal L3 (RPL3L).

74. A method for identifying compounds which bind to human ribosomal L3 (RPL3L), said method comprising a competitive binding assay wherein the cells according to claim 68 are exposed to a plurality of compounds and identifying compounds which bind thereto.

75. Isolated nucleic acid encoding human augmenter of liver regeneration (hALR) or its complement.

76. Isolated nucleic acid according to claim 75, wherein said nucleic acid is mRNA.

77. Isolated nucleic acid according to claim 75, wherein said nucleic acid is DNA comprising the sequence set forth in SEQ ID NO:33.

78. Isolated nucleic acid that hybridizes under stringent conditions to the nucleic acid of claim 75.

79. Isolated nucleic acid according to claim 78, comprising the sequence: 5'-TGGCCCAGTTCATACATTTA-3' (SEQ ID NO:69).

80. Isolated nucleic acid according to claim 78, comprising the sequence: 5'-TTACCCCTGTGAGGAGTGTG-3' (SEQ ID NO:70).

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81. An antisense oligonucleotide that specifically binds to and modulates translation of mRNA according to claim 76.

82. Isolated human augmenter of liver regeneration (hALR) and biologically active fragments thereof.

83. Isolated hALR according to claim 82 comprising the amino acid sequence set forth in SEQ ID NO:34.

84. A vector comprising the isolated nucleic acid of claim 75.

85. A host cell comprising the vector of claim 84.

86. A method for producing human augmenter of liver regeneration (hALR), said method comprising:

(a) culturing the host cell of claim 85 in a medium and under conditions suitable for expression of said protein, and

(b) isolating said expressed protein.

87. An antibody that specifically binds to human augmenter of liver regeneration (hALR).

88. A composition comprising an amount of the oligonucleotide according to claim 81, effective to modulate expression of hALR by passing through a cell membrane and binding specifically with mRNA encoding hALR in the cell so as to prevent its translation and an acceptable hydrophobic carrier capable of passing through a cell membrane.

BNSDOCID: <WO___9748797A1_I_>

89 . A composition comprising an amount of the antibody according to claim 87, effective to block binding of naturally occurring ligands to hALR and an acceptable carrier.

90 . A transgenic non-human mammal expressing DNA encoding human augmenter of liver regeneration (hALR).

91 . A method for identifying compounds which bind to human augmenter of liver regeneration (hALR), said method comprising a competitive binding assay wherein the cells according to claim 85 are exposed to a plurality of compounds and identifying compounds which bind thereto.

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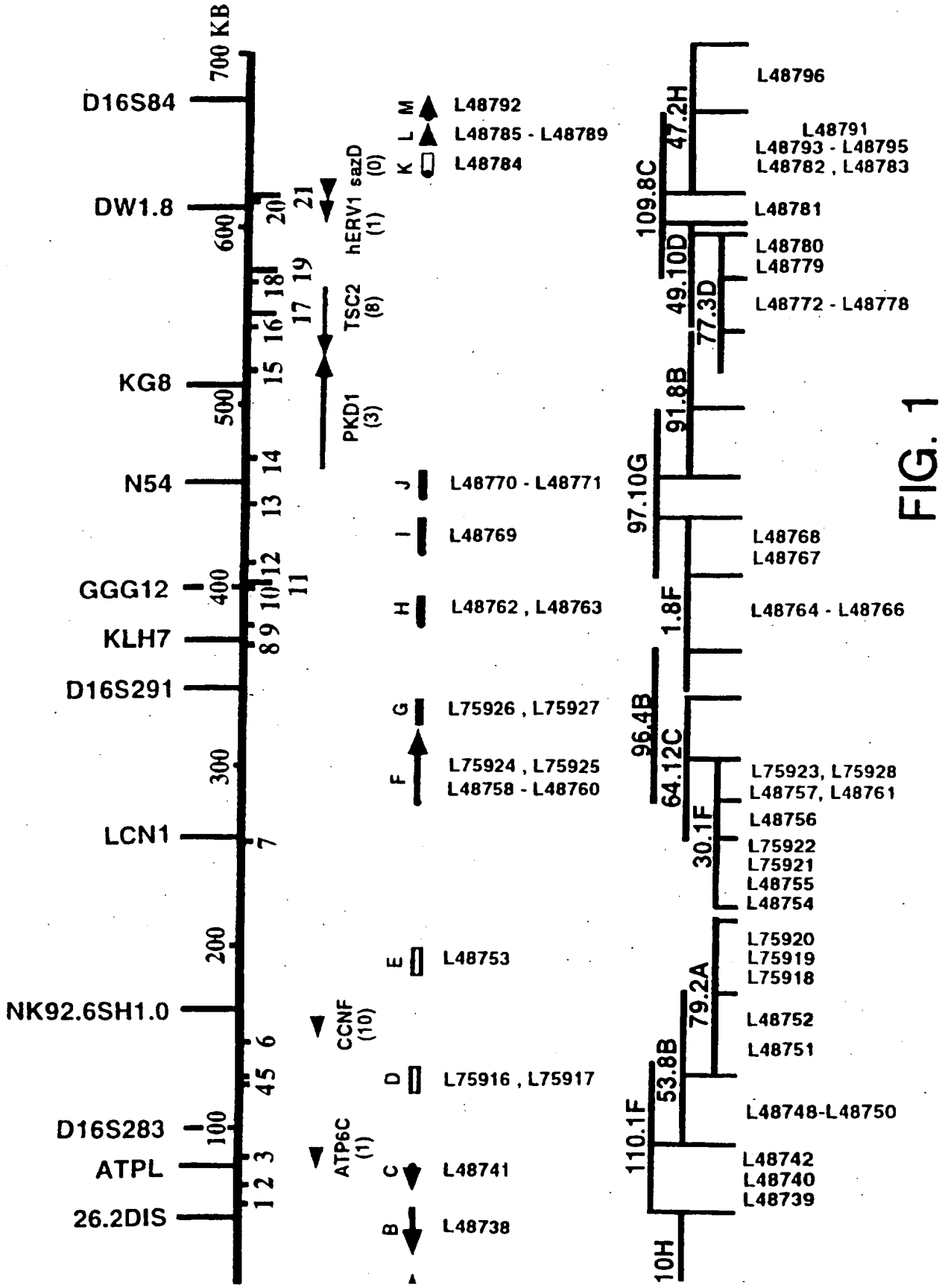

FIG. 1

BNSDOCID: <WO___9748797A1_I_>

8741

```
n Trap          LHLEGPFISREKRGTHPEAHLRSFEADAFQDLLATYGPLDNVRIVTLDPELGRSHEVFRTLTXRSICVSLGHSVADLRAAEDAVWSGATF
elegans    150  -HLEGPFIS--KRG-HPE----S----------YG---N--IVT--PEL----E----------VS-GHS-A-L---E-AV-SGA--
coli       128  LHLEGP-----K-GTH-----R---A-A--D-L------D----VTL-PE-----EV---L----I-VS-GHS-A-L--A------G-TF
influenza  126  LH-E-P--S-EK-G-H-----R--------D-L---G--D-----T---E--------------I-VS-GHS-A----A--A---GATF

n Trap          ITHLFNAMLPFHHRDPGIVGLLTSDRLPAGRCIFYGMIADGTHTNPAALRIAHRAHPQGLVLVTDAIPALGLGNGRHTLGQQEVEVDGLT
elegans    242  ITHLFNAM---HHRDPG--GLLTS--L-------YG-I-DG-HT---ALRIA------GLVLVTDAI-ALG---G-H-LG-Q---V-GL-
coli       213  -THL-NAM-P---------GL-----L-----I--G-IADG-H---A--R-A-R-----L-LVTDA----G----------
influenza  211  -THL-NAM-P---------G--------------G-I-DG-H-N----RI--------L--VTD-I-A---G-----L-------G-T
```

5917

```
n Trap          CDCHPVGAAGKTCNQTTGQCPCKDGVTGLTCNRCAPGFQQSRSPVAPCV
rin-2      381  CDCHPVGAAGKTCNQTTGQCPCKDGVTGLTCNRCAKGFQQSRSPVAPC-
rin-1      406  CDCHPVGAAG-TCNQTTGQCPCKDGVTG-TCNRCAKG-QQSRSP-APC-
-6:        410  C-CHPVG--G--CNQ--GQC-CK-GVTG-TCNRCAKG-QQSRS-V-PC-
```

FIG. 2A

BNSDOCID: <WO 9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

.75916

```
xon Trap          HSPSLSAETPIPGPTEDSSPVQPQDCDSHCKPARGSYRISLKKFCKKDY
etrin-2    425    ----------I--------S---P-DCDS-CKPA-G-Y-I--KK-CKKDY
etrin-1    450    -----------P-PT--SS---P-DCDS-CK---G---I--KK-CKKDY
```

.48770-48771

```
AB26 RT-PCR       MLVGDSGVGKTCLLVRFKDGAFLAGTFISTVGIDFRNKVLDVDGVKAKLQMWDTAGQERFRSVTHAYYRDAHALLLLYDVTNKASFDN
at Rab26       1  MLVGDSGVGKTCLLVRFKDGAFLAGTFISTVGIDFRNKVLDVDG-K-KLQ-WDTAGQERFRSVTHAYYRDAHALLLLYD-TNK-SFDN
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.48792

```
xon Trap          FQNHFEPGVYVCAKCGYELFSSRSKYAHSSPWPAFTETIHADSVAKRPEHNRSEALKV·SCGKCGNGLGHEFLNDGPKPGQSRF
ilB Protein  410  ----F-PG-YV----G--LFSS--KY-----WP-FT--I-A-SV-------------V·---------LGH-F--DGP-------
. cerevisiae  68  -----E-GVY-CA-CD--L-SS--K------WPAF-E-----------------A-----C--C---LGH-F---G-K------
.elegans      55  F--HFE-G-YVC--CG-ELF-S--K------WPAF-E--------------------V·-C--C---LGH-F-NDGPK------
.infuenza    241  ----F--G-YV----G---FSS--K------WP-FT--I--D-V-------------·-----GN-LGH-F--DGPK-G--R-
```

FIG. 2B

```
   1  GGAGCTCGGTTGGAAACCCCCCGAGGCATAATAGGCGCTCGATAAATGTGCAATAGGTGAACATGTGGTGGC
  73  TTGCAGGCGTCTGGGGGGAGACAGCAGGTTCTGGGCTGGGCAGGGAATTATTGGATCAACGGGCATCTTACA
 145  GGAAAGACTCTCAGCTCCCTGCCGCCTAGGACTGTCCAGCCCATCTATGCCCTCTCCCCAGCCTGTGCCCCA
 217  AAGCTGGAGCTGCCACTCTAGGGGTGAGGGGTGGGGTGGGGAGGGGGAGGCGAAGCACTGCGGCCTGAGTTG
 289  CAGGTGGGGGGAGGGGAGGCGGAGCTTCTTTGTTGCAGAAGGTGCCAGGAGGGGGCAGGGCCAGTGGAGAGG
 361  TGGGAGGTGGGAGAGGCCCCAGCCAGGGGCTGGGACAGGTGGCTGGGTCCCTGGGGAGCAATAAGTCCCGCT
 433  TGGGCGCTGTGGGGAGGCCCTTCCTAACTCCCAAACACCATCTGTGAGGGCTGGGGGTGGGGGCAGAGTAGC
 505  GTGTGCAGAGGACTGTTCCTGGGGAGAGGCCCTGTGACCAGCGGCCTCCTCCCTGGGGAGCTGGCGGTACAA
 577  TGGCCCTCTGGGCCCACGGCCTCCCGCCGCTGCTGCTGACCCAGATGAACAATTGGGGCAGGGCTGAGCCCC
 649  AGGCACCTACTTTCCCCCACCCCAGAAGCCACCAGACGTTCTGCAGACCCCAGTCCTGGCTCACAGGGAAGC
 721  TGAGCTGGAGACAAAGCCAGCCCCTCTGATGAGGGTGGAAGAGGCTGCTGGCCACTGTCCCTCTTGCAGCCT
 793  GGCTGGCAGCCAGTCTGGCAGTGGCCCTGACGTCCAGAGACAGCTTGGGTTTCCCCAGAGGCTTGTCTCTGG
 865  CCAGTGGGACCCCTCTGTCAGGCCTGGGCTTTTCTCTCCACTGTCCCAGAATGATGATCTCAGCCCCCATAG
 937  TCCCCCCAGGGTTCCTCCCACCCTTAGGGTGGGGTGTCGGGGGGTGGGGGTTGGGAGCCAGAAGGACCTTGA
1009  AGAGGGTGGTTGGGACGTTTCAGGTTCTAAGCTTGACCCACAGAGCGGAGCGTGAGCCCCGTCAGGTTGAGG
1081  TCCCTCAACTTGTAAAGGACACAATTCCATTCTCTTTATCAGGAAGCTGAGGGGCAGGGGCCCTGTGGCAGA
1153  GAGAGAGCCCCTTAGCCCTCTCTGTTCAGTCCTCCGGTGCCCCCATCCCTGTGCATCTGTGGCTGTCACATG
1225  CAGATGTGTGGCAAGGAGAAGGTGCCCACCAGCCAGTGTCAGTTGCTCCAGGAGCCAAGCCAGGTGCCCTAT
1297  CACCCTGTCTTCCCGTTCCTCCCCTCCATGGTCAGGCCCTCCTGCTCCCTCCTCTGGTCCTTCAGTTTCCCC
1369  TAGGAGGCTTCCGTGTCCTCCTGCCCCTCCTCTCCCCAACAGCGGGATGCGTCTACCTCTCCATTCTCTTCC
1441  TCCTGGTCCTTGCTCATCTCTGGTCGTGTCCAGGGTAGCACCCACGTGGCCTCCTCCACCAGCTGCAGGCCT
1513  GGCCTCCCATCTGAAACGGGGCATTCAGGCCTCGATGCTGGCCCTGCACGGAACTTGTTCCCTGCCCCTCCC
1585  TGGGATGCTTGGCCTCCTCTGTCAAGGACCTGAAAGTCGGAGGGGAGGAGGTTTCTCTGACCAGAGCTGTTC
1657  CTGGACCCTCTTTGGTGGTGTCGCTCCCAGGCACAGCTACCCCATCCCCAGCTAGTCCCCAGGCCACCCAGC
1729  TGGGCTTCTGCCTCAGTTTCCCTGCCCAAACGTGCTGTGACGTAGGGCAGTGGGCTCCGGGTTGCGACCAGC
1801  CCCTTCCCATGATTAAACCCTACTCCCTGCCCCTGCAGAGGGGTCCTCAACAGCTAACCAAGCCCCCGAACC
1873  CCAAGAAGCCACCCCATCCCACCCTCCAGCTTCCATGTCCTCCCTGCCAGCTGGGCCCGTGGCAGAGGTGCC
1945  CCTAGAAACTTGCAGACCCAGGGAGCTTTGGGATCAGAATCTGGCCTGGTGCAGGGGATGCTGGCCTCATGT
2017  CTTAGCCCAGCTCAGGCCCATGGGGGTGCCCCCCTTCCTCAACATGGGCAGGAGACACTCCAATTTGTGCAG
2089  CTCTCGACTTGGGCCTGATGCCACTTGAGACTCATCAAATCCAACAGCTTCAGAGCGCGTGCTGAGTAACAG
2161  GCATCTGGCAGGTGAGGAAACAGGAGCCCAAGACATGCAGCCAGAAATGGGGCAGTTGGATTCAAAATTAGA
2233  CCTGACCGAATCCTGGGTTCCTTCTACTCGAGTAGATGCTGCTTTGGGGATGACCCTTCAACTGGTGGTTAC
2305  TTGGCTTCCCTACCTGGGGAACATCCAGGGCCTCTGCTGTCAGACCCGGGGCCTTGCCTGCCTGATGGTCTT
2377  CAGGGAGGAGGCGACCCAGACCCCCGTCCAGCACGTGGCACAGCCCCAGGAGCAGTAAAGACCTGGCTGTGG
2449  GCCCAGGACCCTGCTGGGTGGTCCCCCACGGGCTGCGAAGGCTGAGCTGCCCCCCTCCAGACCCCTCCCGCC
2521  AGCGCATTCCTGGCTCCCCGGCCCCTCCCCTGGCTCCCGGGCCTCCCAGCCCCCTTCCCCGCTGGCCCAGCC
2593  CGCGTCTGAATCTGCTTCTGATTCCAGCTCTGCGATGAGGCCCCCTCCCCTCCCCTGCCTCCTTCCCGACCC
2665  GAGCAGCCCCGCCCCCGGCTGGGCCCGGGCTTGCGCCTGCTGGCCCCCCACCCCCTCCTGGCACAGCTCGT
2737  CCGCCCTCGCTGCAGCCGGGAGGAGGCGGCGGCCCGTGCACCGCAGGCCCCGCCCGCCCACGGCCCTTCCCG
2809  GGAGGCCGGGAGACCTGCTCCGCCCGGCCCTCGGTGGGTGAGTGCGAGCGGCGGGTGGGGCCTCCGCGGGCG
```

FIG. 3A

BNSDOCID: <WO___9748797A1_I_>

2881 GAGGCACCGGGAGCGGGGGGCGACGCCTGTCATCGCTCTAGGCCCAGCGGGAGGACGCGCCAACATCCCCGCT
2953 GCTGTGCTGGGCCCGGGGCGTGCCCGCCGCTGCTCCCACCTCTGGGCCGGGCTGGGGCCGCCCGGGGGCCCT
3025 GTTCCTCGGCATTGCGGGCCTGGTGGGCAGAGCCGCGGAGAGGCTTCTTTCCCCAAGGGCAGCGTCTTGG
3097 GGCCCGGCCACTGGCTGACCGCAGCGGCTCCGGCCATGCCTGGCTGGCCCTGGGGCTGCTGCTGACGGCA
3169 GGCACGCTCTTCGCCGCCCTGAGTCCTGGGCCGCCGGCGCCCGCCGACCCCTGCCACGATGAGGGGGTGCG
3241 CCCCGCGGCTGCGTGCCAGGACTGGTGAACGCCGCCCTGGGCCGCGAGGTGCTGGCTTCCAGCACGTGCGGG
3313 CGGCCGGCCACTCGGGCCTGCGACGCCTCCGACCCGCGACGGGCACACTCCCCCGCCCTCCTTACTTCCCCA
3385 GGGGGCACGGCCAGCCCTCTGTGCTGGCGCTCGGAGTCCCTGCCTCGGGCGCCCCTCAACGTGACTCTCACG
3457 GTGCCCCTGGGCAAGGCTTTTGAGCTGGTCTTCGTGAGCCTGCGCTTCTGCTCAGCTCCCCCAGCCTCCGTG
3529 GCCCTGCTCAAGTCTCAGGACCATGGCCGCAGCTGGGCCCCGCTGGGCTTCTTCTCCTCCCACTGTGACCTG
3601 GACTATGGCCGTCTGCCTGCCCCTGCCAATGGCCCAGCTGGCCCAGGGCCTGAGGCCCTGTGCTTCCCCGCA
3673 CCCCTGGCCCAGCCTGATGGCAGCGGCCTTCTGGCCTTCAGCATGCAGGACAGCAGCCCCCCAGGCCTGGAC
3745 CTGGACAGCAGCCCAGTGCTCCAAGACTGGGTGACCGCCACCGACGTCCGTGTAGTGCTCACAAGGCCTAGC
3817 ACGGCAGGTGACCCCAGGGACATGGAGGCCGTCGTCCCTTACTCCTACGCAGCCACCGACCTCCAGGTGGGC
3889 GGGCGCTGCAAGTGCAATGGACATGCCTCACGGTGCCTGCTGGACACACAGGGCCACCTGATCTGCGACTGT
3961 CGGCATGGCACCGAGGGCCCTGACTGCGGCCGCTGCAAGCCCTTCTACTGCGACAGGCCATGGCAGCGGGCC
4033 ACTGCCCGGGAATCCCACGCCTGCCTCGGTGAGGCCTTGGAGGGTGGCCTGGGGACCTTGGACACAACCAGC
4105 CTGCCCCTGACCCATCCCTCCCTGCAGCTTGCTCCTGCAACGGCCATGCCCGCCGCTGCCGCTTCAACATGG
4177 AGCTGTACCGACTGTCCGGCCGCCGCAGCGGGGGTGTCTGTCTCAACTGCCGGCACAACACCGCCGGCCGCC
4249 ACTGCCACTACTGCCCGGGAGGCTTCTATCGAGACCCTGGCCGTGCCCTGAGTGACCGTCGGGCTTGCAGGG
4321 GTGAGCCACCACCGGCCACCTGCAGGCCCTCACCCTCTGACTTCCCAGATCCCCAGACAGGCTTCTGACCAG
4393 GCCCTTCCCACCTCTGTCCTCAGCCTGCGACTGTCACCCGGTTGGTGCTGCTGGCAAGACCTGCAACCAGAC
4465 CACAGGCCAGTGTCCCTGCAAGGATGGCGTCACTGGCCTCACCTGCAACCGCTGCGCGCCTGGCTTCCAGCA
4537 AAGCCGCTCCCCAGTGGCGCCCTGTGTTAGTGAGTGACCCTGCCCCGCCTCAGCCACCAAGCCAAGGCCACC
4609 CCAGCTCCCTGCTGTTGTCCCGTCTATTCCCCGAGCCCTGCAGATCTCTCTGCCCCTCCATCGCAGGCCATT
4681 CTCCCTCCCTCTCTGCAGAGACCCCTATCCCTGGACCCACTGAGGACAGCAGCCCTGTGCAGCCCCAGGGTG
4753 AGTGGACACAGGACAGGGCCCCAGACTGGCATGACTTTGGGGGAGGGGGCTCTGGGAGGAGAGGGTGGGGAA
4825 AGGGAGTCTGTGCCAGCCTCCCACCTTCTACCCAGACTGTGACTCGCACTGCAAACCTGCCCGTGGCAGCTA
4897 CCGCATCAGCCTAAAGAAGTTCTGCAAGAAGGACTATGGTAGGTGCCCTCAGGCCTCCCGCGGACCTTCCCA
4969 CCTTCCTCCTCTCCCTACCTTCCCTCCTCCGCCAGCTTCCCCTTGGAACGCCTTGACCCTTGCTGGGCCCCA
5041 AGGCCCATCCTCATCCCTCAGGTCCTCCACGGGCAGCGACCCCGCCCCTTCAGCCCCCACTGCCCTCCTGGT
5113 GTCCTCCCCGTGCCTCCCCCTACCGCGGGCAGGCCGCCCCTTCCTGACCCCGCCCCCTCTGCTCTCCCCGC
5185 AGCGGTGCAGGTGGCGGTGGGTGCGCGCGGCGAGGCGCGCGGCGCGTGGACAGCTTCCCGGTGGCGGTGCT
5257 CGCCGTGTTCCGGAGCGGAGAGGAGCGCGCGCGGCGCGGGAGTAGCGCGCTGTGGGTGCCCGCCGGGGATGC
5329 GGCCTGCGGCTGCCCCGCGCCTGCTCCCCGGCCGCGGCTACCTCCTGCTGGGGGCGGGCCTGGAGCCCGGC
5401 TGGGGGCGCGGGGGGCCGGGGGCCCGGCTCATCGCCGCCCGCGGAAGCCTCGTGCTACCCTGGAGGGACGC
5473 GTGGACGCGGCGCCTGCGGAGGCTGCAGCGACGCGAACGGCGGGGGCGCTGCAGCGCCGCCTGAGCCCGCG
5545 GCTGGGCAGGGCGGCCGCTGCTCCCACATCTAGGCGCACGTTCACCCTGTGCCTTCGCCTGCCAAGGAGTCC
5617 TTGCTCGCGTCGCGCGTGTCGCCACCTGGGCCGCCGCCCCGTCCCCGCCGGCAGCTCCCTCGGTACCTCCCG
5689 TCTGGCCCTGGGGGGATGTGACCGGCGCACGGACAGCCCGCCCCGCACAGAGGCAGATGATATGGCACACCC

FIG. 3B

BNSDOCID: <WO___9748797A1_I_>

5761 GGAGGACCCCATGGTCTCCCGCCCTCTGGCTGTCGGCCCTGTCCCAGGGGCACTGGGATACCCGGAAGGCTG
5833 TGAATCCTTCGTGATGCCGGGCCCTCTCGGGGATCTCAGATCATCCCCGGGGCCGCTGTGATGCACCCCCAC
5905 CTGTGCGGCGACCCGCCAGGAGCGCACTGACCTCCCCAAAGACTGTGGCCACCGCAGGCGCCTTGGACCCCC
5977 ATGGGGGACAGGGCGTCCCCTGCCTCCTGCAGCCCCACGAGGGCGGCGGCCTTGGCCCTGCGGCTGGGCGTC
6049 CGCGTCCGGGCGCCCCGCGGCGTCTGCTGCCGGGTCCCGTAACTTTCTTGGCCGCCTGTGTCCCCGTCTGCC
6121 GGCTCCGTCCGGCCGTCCCTCTCTCTGCCCGCGTCTCTGACCCTCGGCGCCACAGCTCCTCAGCTCAGGCCC
6193 GTCCCAGAACCTCCTTCCAGCCCTTCTCCCCCGACTCGGGAAGGGACGTCGTGCCCACGCGGTTCCGGATCC
6265 ACGCGTGACCCGGCCCGACCCGGACTCCGACAGGCGGCTGTCCGGGCCCCCGATGCCCTCGGCAGGCCCGTG
6337 CCACCCCCCGCCCCTTGTTGTCCCCCCGGGACCGGCACTGCCGTTTGCCTCCTCTCCGCACGGGACCGGTTC
6409 CCGGCCGGCCCCAGCTTCCGCCGCTGCGGCCGCCGACCGTCAGCGGCATGCCCAGAGCCGGGCAGGCCCGA
6481 GCCCCGCCGGCTCTCCGGGGTGGGCACAGGGCGACAGCTCGGCGGGGCGGGGCCGAGCACGCGGTGCGCA
6553 GAAAGGCCGGCGCGGCAGGCTGAGGAGAAAGCGGCGCGCGGAGGTGGGTGCGCTCGGGGCGTGCGGGGGCG
6625 CGCGGCGGGGTGGCGGGTGGCGGGGCCGGGTCCCCGCTGTCACCGCGGTCGGCGCGTGCTGGGGCCGGAGC
6697 GTGGGGCCCGGCTGCGTGCCCCATTCGAGGCGGGGATCCCCGCCACGCGCGGGTTGGGGGCTCCAGAGCC
6769 CGGCACCGCCCCGCGCTGCAGCTGCGGCTTGGCCT

FIG. 3C

BNSDOCID: <WO___9748797A1_I_>

```
1   ATGCCTGGCTGGCCCTGGGGGCTGCTGCTGACGGCAGGCACGCTCTTCGCCGCCCTGAGTCCTGGGCCGCC
      M  P  G  W  P  W  G  L  L  L  T  A  G  T  L  F  A  A  L  S  P  G  P  P
72  GGCGCCCGCCGACCCCTGCCACGATGAGGGGGGTGCGCCCCGCGGCTGCGTGCCAGGACTGGTGAACGCCG
      A  P  A  D  P  C  H  D  E  G  G  A  P  R  G  C  V  P  G  L  V  N  A
143 CCCTGGGCCGCGAGGTGCTGGCTTCCAGCACGTGCGGGCGGCCGGCCACTCGGGCCTGCGACGCCTCCGAC
      A  L  G  R  E  V  L  A  S  S  T  C  G  R  P  A  T  R  A  C  D  A  S  D
214 CCGCGACGGGCACACTCCCCCGCCCTCCTTACTTCCCCAGGGGGCACGGCCAGCCCTCTGTGCTGGCGCTC
      P  R  R  A  H  S  P  A  L  L  T  S  P  G  G  T  A  S  P  L  C  W  R  S
285 GGAGTCCCTGCCTCGGGCGCCCCTCAACGTGACTCTCACGGTGCCCCTGGGCAAGGCTTTTGAGCTGGTCT
      E  S  L  P  R  A  P  L  N  V  T  L  T  V  P  L  G  K  A  F  E  L  V
356 TCGTGAGCCTGCGCTTCTGCTCAGCTCCCCCAGCCTCCGTGGCCCTGCTCAAGTCTCAGGACCATGGCCGC
      F  V  S  L  R  F  C  S  A  P  P  A  S  V  A  L  L  K  S  Q  D  H  G  R
427 AGCTGGGCCCCGCTGGGCTTCTTCTCCTCCCACTGTGACCTGGACTATGGCCGTCTGCCTGCCCCTGCCAA
      S  W  A  P  L  G  F  F  S  S  H  C  D  L  D  Y  G  R  L  P  A  P  A  N
498 TGGCCCAGCTGGCCCAGGGCCTGAGGCCCTGTGCTTCCCCGCACCCCTGGCCCAGCCTGATGGCAGCGGCC
      G  P  A  G  P  G  P  E  A  L  C  F  P  A  P  L  A  Q  P  D  G  S  G
569 TTCTGGCCTTCAGCATGCAGGACAGCAGCCCCCCAGGCCTGGACCTGGACAGCAGCCCAGTGCTCCAAGAC
      L  L  A  F  S  M  Q  D  S  S  P  P  G  L  D  L  D  S  S  P  V  L  Q  D
640 TGGGTGACCGCCACCGACGTCCGTGTAGTGCTCACAAGGCCTAGCACGGCAGGTGACCCCAGGGACATGGA
      W  V  T  A  T  D  V  R  V  V  L  T  R  P  S  T  A  G  D  P  R  D  M  E
711 GGCCGTCGTCCCTTACTCCTACGCAGCCACCGACCTCCAGGTGGGCGGGCGCTGCAAGTGCAATGGACATG
      A  V  V  P  Y  S  Y  A  A  T  D  L  Q  V  G  G  R  C  K  C  N  G  H
782 CCTCACGGTGCCTGCTGGACACACAGGGCCACCTGATCTGCGACTGTCGGCATGGCACCGAGGGCCCTGAC
      A  S  R  C  L  L  D  T  Q  G  H  L  I  C  D  C  R  H  G  T  E  G  P  D
```

FIG. 4A

BNSDOCID: <WO___9748797A1_I_>

```
853  TGCGGCCGCTGCAAGCCCTTCTACTGCGACAGGCCATGGCAGCGGGCCACTGCCCCGGGAATCCCACGCCTG
       C  G  R  C  K  P  F  Y  C  D  R  P  W  Q  R  A  T  A  R  E  S  H  A  C
924  CCTCGCTTGCTCCTGCAACGGCCATGCCCGCCGCTGCCGCTTCAACATGGAGCTGTACCGACTGTCCGGCC
       L  A  C  S  C  N  G  H  A  R  R  C  R  F  N  M  E  L  Y  R  L  S  G
995  GCCGCAGCGGGGGTGTCTGTCTCAACTGCCGGCACAACACCGCCGGCCGCCACTGCCACTACTGCCCGGAG
       R  R  S  G  G  V  C  L  N  C  R  H  N  T  A  G  R  H  C  H  Y  C  R  E
1066 GGCTTCTATCGAGACCCTGGCCGTGCCCTGAGTGACCGTCGGGCTTGCAGGCCTGCGACTGTCACCCGGT
       G  F  Y  R  D  P  G  R  A  L  S  D  R  R  A  C  R  A  C  D  C  H  P  V
1137 TGGTGCTGCTGGCAAGACCTGCAACCAGACCACAGGCCAGTGTCCCTGCAAGGATGGCGTCACTGGCCTCA
       G  A  A  G  K  T  C  N  Q  T  T  G  Q  C  P  C  K  D  G  V  T  G  L
1208 CCTGCAACCGCTGCGCGCCTGGCTTCCAGCAAAGCCGCTCCCCAGTGGCGCCCTGTGTTAAGACCCCTATC
       T  C  N  R  C  A  P  G  F  Q  Q  S  R  S  P  V  A  P  C  V  K  T  P  I
1279 CCTGGACCCACTGAGGACAGCAGCCCTGTGCAGCCCCAGGACTGTGACTCGCACTGCAAACCTGCCCGTGG
       P  G  P  T  E  D  S  S  P  V  Q  P  Q  D  C  D  S  H  C  K  P  A  R  G
1350 CAGCTACCGCATCAGCCTAAAGAAGTTCTGCAAGAAGGACTATGCGGTGCAGGTGGCGGTGGGTGCGCGCG
       S  Y  R  I  S  L  K  K  F  C  K  K  D  Y  A  V  Q  V  A  V  G  A  R
1421 GCGAGGCGCGCGGCGCGTGGACACGCTTCCCGGTGGCGGTGCTCGCCGTGTTCCGGAGCGGAGAGGAGCGC
       G  E  A  R  G  A  W  T  R  F  P  V  A  V  L  A  V  F  R  S  G  E  E  R
1492 GCGCGGCGCGGGAGTAGCGCGCTGTGGGTGCCCGCCGGGGATGCGGCCTGCGGCTGCCCGCGCCTGCTCCC
       A  R  R  G  S  S  A  L  W  V  P  A  G  D  A  A  C  G  C  P  R  L  L  P
1563 CGGCCGCCGCTACCTCCTGCTGGGGGGCGGGCCTGGAGCCGCGGCTGGGGCGCGGGGGGCGCCGGGGCCCG
       G  R  R  Y  L  L  L  G  G  G  P  G  A  A  A  G  G  A  G  G  R  G  P
1634 GGCTCATCGCCGCCCGCGGAAGCCTCGTGCTACCCTGGAGGGACGCGTGGACGCGGCGCCTGCGGAGGCTG
       G  L  I  A  A  R  G  S  L  V  L  P  W  R  D  A  W  T  R  R  L  R  R  L
1705 CAGCGACGCGAACGGCGGGGGCGCTGCAGCGCCGCCTGA
       Q  R  R  E  R  R  G  R  C  S  A  A  .  .
```

FIG. 4B

BNSDOCID: <WO___9748797A1_I_>

FIGURE 4C

CAGCGGGAGG ACGCGCCAAC ATCCCCGCTG CTGTGCTGGG CCCGGGGCGT GCCCGCCGCT 60

GCTCCCACCT CTGGGCCGGG CTGGGGCCGC CCGGGGGCCC TGTTCCTCGG CATTGCGGGC 120

CTGGTGGGCA GAACCGCGGA GAGGGCTTCT TTTCCCCAAG GGCAGCGTCT TGGGGCCCGG 180

CCACTGGCTG ACCCGCAGCG GCTCCGGCCA TGCCTGGCTG GCCCTGGGGG CTGCTGCTGA 240

CGGCAGGCAC GCTCTTCGCC GCCCTGAGTC CTGGGCCGCC GGCGCCCGCC GACCCCTGCC 300

ACGATGAGGG GGGTGCGCCC CGCGGCTGCG TGCCAGGACT GGTGAACGCC GCCCTGGGCC 360

GCGAGGTGCT GGCTTCCAGC ACGTGCGGGC GGCCGGCCAC TCGGGCCTGC GACGCCTCCG 420

ACCCGCGACG GGCACACTCC CCCGCCCTCC TTACTTCCCC AGGGGGCACG GCCAGCCCTC 480

TGTGCTGGCG CTCGGAGTCC CTGCCTCGGG CGCCCCTCAA CGTGACTCTC ACGGTGCCCC 540

TGGGCAAGGC TTTTGAGCTG GTCTTCGTGA GCCTGCGCTT CTGCTCAGCT CCCCCAGCCT 600

CCGTGGCCCT GCTCAAGTCT CAGGACCATG GCCGCAGCTG GGCCCCGCTG GGCTTCTTCT 660

CCTCCCACTG TGACCTGGAC TATGGCCGTC TGCCTGCCCC TGCCAATGGC CCAGCTGGCC 720

CAGGGCCTGA GGCCCTGTGC TTCCCCGCAC CCCTGGCCCA GCCTGATGGC AGCGGCCTTC 780

TGGCCTTCAG CATGCAGGAC AGCAGCCCCC CAGGCCTGGA CCTGGACAGC AGCCCAGTGC 840

TCCAAGACTG GGTGACCGCC ACCGACGTCC GTGTAGTGCT CACAAGGCCT AGCACGGCAG 900

GTGACCCCAG GGACATGGAG GCCGTCGTCC CTTACTCCTA CGCAGCCACC GACCTCCAGG 960

TGGGCGGGCG CTGCAAGTGC AATGGACATG CCTCACGGTG CCTGCTGGAC ACACAGGGCC 1020

BNSDOCID: <WO___9748797A1_I_>

FIGURE 4D

ACCTGATCTG CGACTGTCGG CATGGCACCG AGGGCCCTGA CTGCGGCCGC TGCAAGCCCT 1080

TCTACTGCGA CAGGCCATGG CAGCGGGCCA CTGCCCGGGA ATCCCACGCC TGCCTCGCTT 1140

GCTCCTGCAA CGGCCATGCC CGCCGCTGCC GCTTCAACAT GGAGCTGTAC CGACTGTCCG 1200

GCCGCCGCAG CGGGGGTGTC TGTCTCAACT GCCGGCACAA CACCGCCGGC CGCCACTGCC 1260

ACTACTGCCG GGAGGGCTTC TATCGAGACC CTGGCCGTGC CCTGAGTGAC CGTCGGGCTT 1320

GCAGGGCCTG CGACTGTCAC CCGGTTGGTG CTGCTGGCAA GACCTGCAAC CAGACCACAG 1380

GCCAGTGTCC CTGCAAGGAT GGCGTCACTG GCCTCACCTG CAACCGCTGC GCGCCTGGCT 1440

TCCAGCAAAG CCGCTCCCCA GTGGCGCCCT GTGTTAAGAC CCCTATCCCT GGACCCACTG 1500

AGGACAGCAG CCCTGTGCAG CCCCAGGACT GTGACTCGCA CTGCAAACCT GCCCGTGGCA 1560

GCTACCGCAT CAGCCTAAAG AAGTTCTGCA AGAAGGACTA TGCGGTGCAG GTGGCGGTGG 1620

GTGCGCGCGG CGAGGCGCGC GGCGCGTGGA CACGCTTCCC GGTGGCGGTG CTCGCCGTGT 1680

TCCGGAGCGG AGAGGAGCGC GCGCGGCGCG GGAGTAGCGC GCTGTGGGTG CCCGCCGGGG 1740

ATGCGGCCTG CGGCTGCCCG CGCCTGCTCC CCGGCCGCCG CTACCTCCTG CTGGGGGGCG 1800

GGCCTGGAGC CGCGGCTGGG GGCGCGGGGG GCCGGGGGCC CGGGCTCATC GCCGCCCGCG 1860

GAAGCCTCGT GCTACCCTGG AGGGACGCGT GGACGCGGCG CCTGCGGAGG CTGCAGCGAC 1920

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BNSDOCID: <WO___9748797A1_I_>

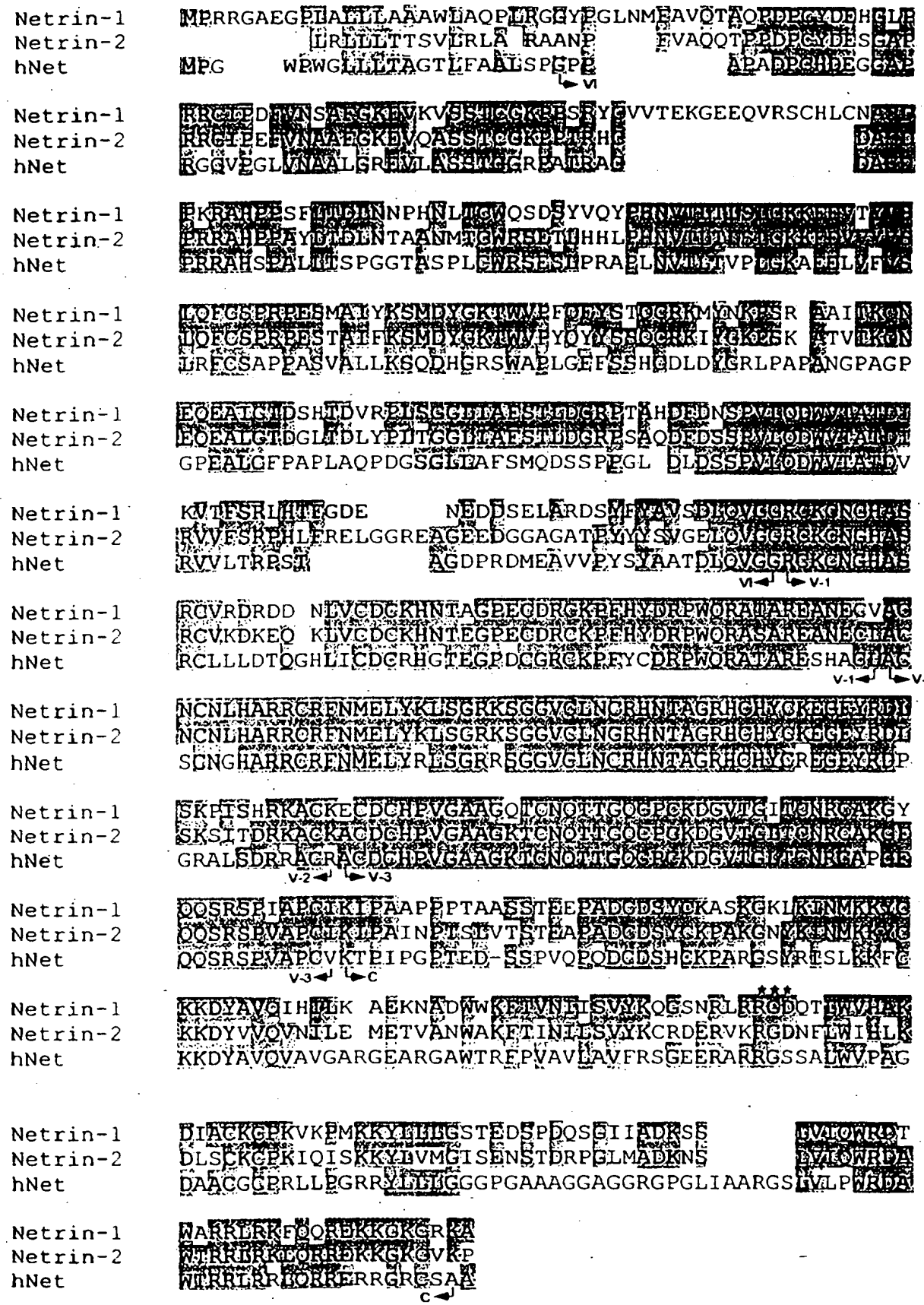

FIG. 5

SUBSTITUTE SHEET (RULE 26)

BNSDOCID: <WO___9748797A1_I_>

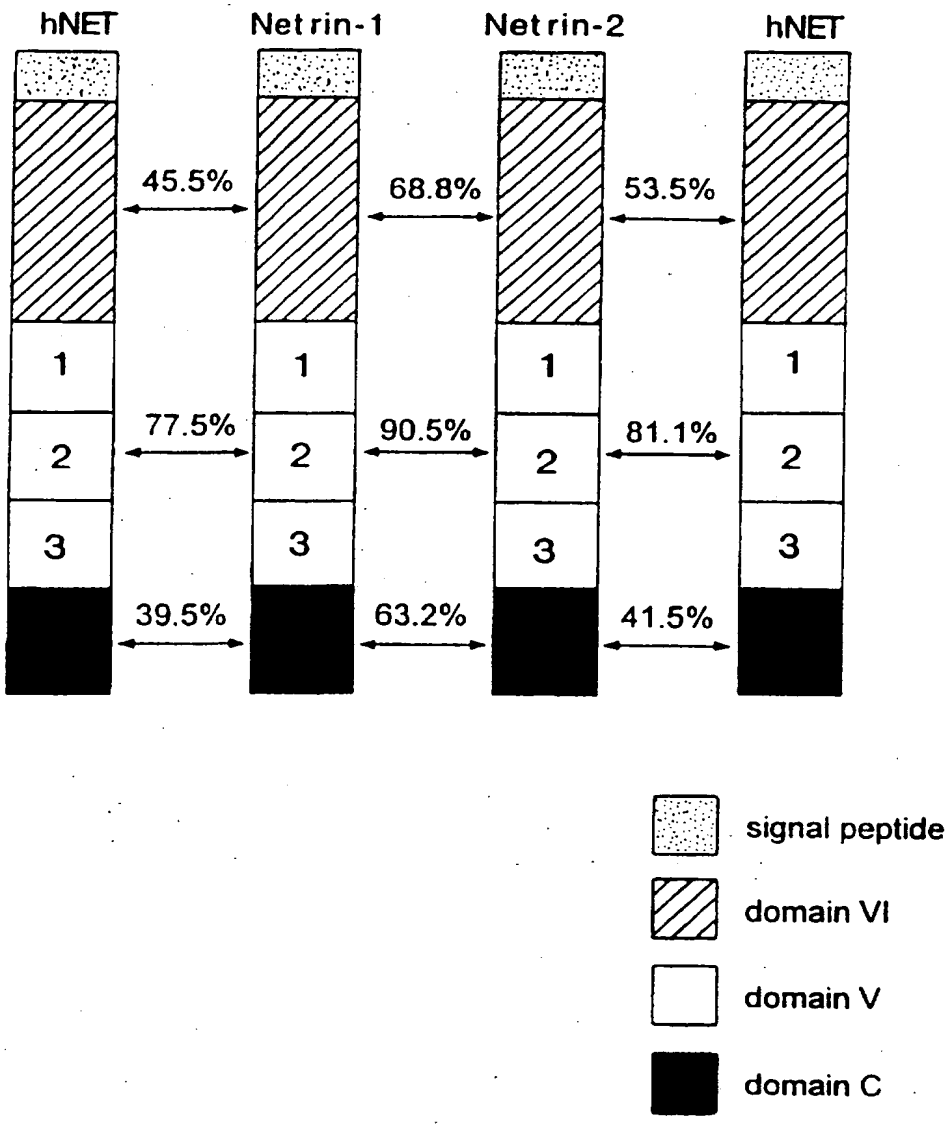

FIG. 6

BNSDOCID: <WO___9748797A1_I_>

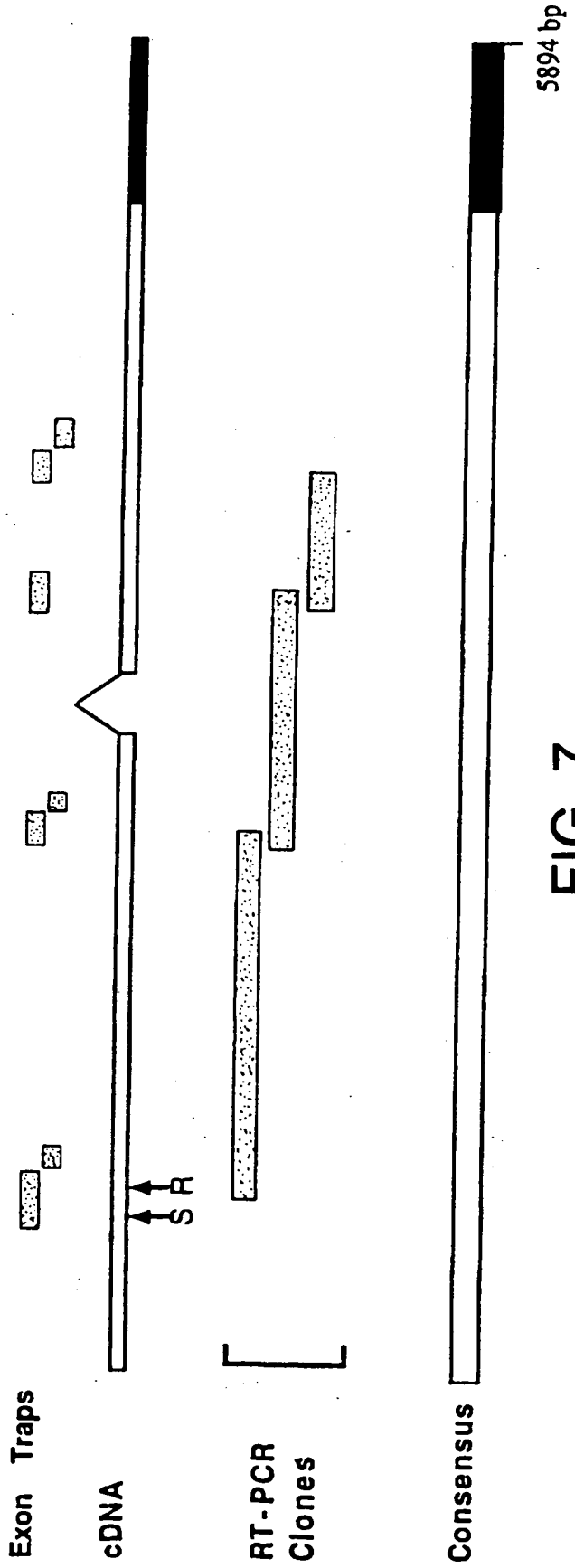

FIG. 7

BNSDOCID: <WO___9748797A1_I_>

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
1
G AAG GTC CTG GTG ACG GTC CTG GAA CTC TTC CTG CCA TTG CTG TTT TCT GGG ATC CTC ATC TGG CTC CGC TTG AAG ATT CAG TCG GAA
  K   V   L   V   T   V   L   E   L   F   L   P   L   L   F   S   G   I   L   I   W   L   R   L   K   I   Q   S   E

                100
AAT GTG CCC AAC GCC ACC ATC TAC CCG GGC CAG TCC ATC CAG GAG CTG CCT CTG TTC TTC ACC TTC CCT CCG CCA GGA GAC ACC TGG GAG
N   V   P   N   A   T   I   Y   P   G   Q   S   I   Q   E   L   P   L   F   F   T   F   P   P   P   G   D   T   W   E

                        200
CTT GCC TAC ATC CCT TCT CAC AGT GAC GCT GCC AAG GCC GTC ACT GAG ACA GTG CGC AGG GCA CTT GTG ATC AAC ATG CGA GTG CGC GGC
L   A   Y   I   P   S   H   S   D   A   A   K   A   V   T   E   T   V   R   R   A   L   V   I   N   M   R   V   R   G

                                300
TTT CCC TCC GAG AAG GAC TTT GAG GAC TAC ATT AGG TAC GAC AAC TGC TCG TCC AGC GTG CTG GCC GCC GTG GTC TTC GAG CAC CCC TTC
F   P   S   E   K   D   F   E   D   Y   I   R   Y   D   N   C   S   S   S   V   L   A   A   V   V   F   E   H   P   F

                                        400
AAC CAC AGC AAG GAG CCC CTG CCG CTG GCG GTG AAA TAT CAC CTA CGG TTC AGT TAC ACA CGG AGA AAT TAC ATG TGG ACC CAA ACA GGC
N   H   S   K   E   P   L   P   L   A   V   K   Y   H   L   R   F   S   Y   T   R   R   N   Y   M   W   T   Q   T   G

                                                500
TCC TTT TTC CTG AAA GAG ACA GAA GGC TGG CAC ACT ACT TCC CTT TTC CCG CTT TTC CCA AAC CCA GGA CCA AGG GAA CTA ACA TCC CCT
S   F   F   L   K   E   T   E   G   W   H   T   T   S   L   F   P   L   F   P   N   P   G   P   R   E   L   T   S   P

                                                        600
GAT GGC GGA GAA CCT GGG TAC ATC CGG GAA GGC TTC CTG GCC GTG CAG CAT GCT GTG GAC CGG GCC ATC ATG GAG TAC CAT GCC GAT GCC
D   G   G   E   P   G   Y   I   R   E   G   F   L   A   V   Q   H   A   V   D   R   A   I   M   E   Y   H   A   D   A
```

FIG. 8A

```
                                                                    700
GCC ACA CGC CAG CTG TTC CAG AGA CTG ACG GTG ACC ATC AAG AGG TTC CCG TAC CCG CCG TTC ATC GCA GAC CCC TTC CTC GTG GCC ATC
A   T   R   Q   L   F   Q   R   L   T   V   T   I   K   R   F   P   Y   P   P   F   I   A   D   P   F   L   V   A   I

                                                                                                    800
CAG TAC CAG CTG CCC CTG CTG CTG CTG CTC AGC TTC ACC TAC ACC GCG CTC ACC ATT GCC CGT GCT GTC GTG CAG GAG AAG GAA AGG AGG
Q   Y   Q   L   P   L   L   L   L   L   S   F   T   Y   T   A   L   T   I   A   R   A   V   V   Q   E   K   E   R   R

CTG AAG GAG TAC ATG CGC ATG ATG GGG CTC AGC AGC TGG CTG CAC TGG AGT GCC TGG TTC CTC TTG TTC TTC CTC TTC CTC CTC ATC GCC
L   K   E   Y   M   R   M   M   G   L   S   S   W   L   H   W   S   A   W   F   L   L   F   F   L   F   L   L   I   A

00
GCC TCC TTC ATG ACC CTG CTC TTC TGT GTC AAG GTG AAG CCA AAT GTA GCC GTG CTG TCC CGC AGC GAC CCC TCC CTG GTG CTC GCC TTC
A   S   F   M   T   L   L   F   C   V   K   V   K   P   N   V   A   V   L   S   R   S   D   P   S   L   V   L   A   F

                1000
CTG CTG TGC TTC GCC ATC TCT ACC ATC TCC TTC AGC TTC ATG GTC AGC ACC TTC TTC AGC AAA GCC AAC ATG GCA GCA GCC TTC GGA GGC
L   L   C   F   A   I   S   T   I   S   F   S   F   M   V   S   T   F   F   S   K   A   N   M   A   A   A   F   G   G

                        1100
TTC CTC TAC TTC TTC ACC TAC ATC CCC TAC TTC TTC GTG GCC CCT CGG TAC AAC TGG ATG ACT CTG AGC CAG AAG CTC TGC TCC TGC CTC
F   L   Y   F   F   T   Y   I   P   Y   F   F   V   A   P   R   Y   N   W   M   T   L   S   Q   K   L   C   S   C   L

                                1200
CTG TCT AAT GTC GCC ATG GCA ATG GGA GCC CAG CTC ATT GGG AAA TTT GAG GCG AAA GGC ATG GGC ATC CAG TGG CGA GAC CTC CTG AGT
L   S   N   V   A   M   A   M   G   A   Q   L   I   G   K   F   E   A   K   G   M   G   I   Q   W   R   D   L   L   S

                                        1300
CCC GTC AAC GTG GAC GAC GAC TTC TGC TTC GGG CAG GTG CTG GGG ATG CTG CTG CTG GAC TCT GTG CTC TAT GGC CTG GTG ACC TGG TAC
P   V   N   V   D   D   D   F   C   F   G   Q   V   L   G   M   L   L   L   D   S   V   L   Y   G   L   V   T   W   Y
```

FIG. 8B

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

1400

ATG GAG GCC GTC TTC CCA GGG CAG TTC GGC GTG CCT CAG CCC TGG TAC TTC TTC ATC ATG CCC TCC TAT TGG TGT GGG AAG CCA AGG GCG
M E A V F P G Q F G V P Q P W Y F F I M P S Y W C G K P R A

1500

GTT GCA GGG AAG GAG GAA GAA GAC AGT GAC CCC GAG AAA GCA CTC AGA AAC GAG TAC TTT GAA GCC GAG CCA GAG GAC CTG GTG GCG GGG
V A G K E E E D S D P E K A L R N E Y F E A E P E D L V A G

1600

ATC AAG ATC AAG CAC CTG TCC AAG GTG TTC AGG GTG GGA AAT AAG GAC AGG GCG GCC GTC AGA GAC CTG AAC CTC AAC CTG TAC GAG GGA
I K I K H L S K V F R V G N K D R A A V R D L N L N L Y E G

1700

CAG ATC ACC GTC CTG CTG GGC CAC AAC GGT GCC GGG AAG ACC ACC ACC CTC TCC ATG CTC ACA GGT CTC TTT CCC CCC ACC AGT GGA CGG
Q I T V L L G H N G A G K T T T L S M L T G L F P P T S G R

GCA TAC ATC AGC GGG TAT GAA ATT TCC CAG GAC ATG GTT CAG ATC CGG AAG AGC CTG GGC CTG TGC CCG CAG CAC GAC ATC CTG TTT GAC
A Y I S G Y E I S Q D M V Q I R K S L G L C P Q H D I L F D

00

AAC TTG ACA GTC GCA GAG CAC CTT TAT TTC TAC GCC CAG CTG AAG GGC CTG TCA CGT CAG AAG TGC CCT GAA GAA GTC AAG CAG ATG CTG
N L T V A E H L Y F Y A Q L K G L S R Q K C P E E V K Q M L

1900

CAC ATC ATC GGC CTG GAG GAC AAG TGG AAC TCA CGG AGC CGC TTC CTG AGC GGG GGC ATG AGG CGC AAG CTC TCC ATC GGC ATC GCC CTC
H I I G L E D K W N S R S R F L S G G M R R K L S I G I A L

2000

ATC GCA GGC TCC AAG GTG CTG ATA CTG GAC GAG CCC ACC TCG GGC ATG GAC GCC ATC TCC AGG AGG GCC ATC TGG GAT CTT CTT CAG CGG
I A G S K V L I L D E P T S G M D A I S R R A I W D L L Q R

FIG. 8C

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
                                                2100
CAG AAA AGT GAC CGC ACC ATC GTG CTG ACC ACC CAC TTC ATG GAC GAG GCT GAC CTG CTG GGA GAC CGC ATC GCC ATC ATG GCC AAG GGG
Q   K   S   D   R   T   I   V   L   T   T   H   F   M   D   E   A   D   L   L   G   D   R   I   A   I   M   A   K   G

                                                2200
GAG CTG CAG TGC TGC GGG TCC TCG CTG TTC CTC AAG CAG AAA TAC GGT GCC GGC TAT CAC ATG ACG CTG GTG AAG GAG CCG CAC TGC AAC
E   L   Q   C   C   G   S   S   L   F   L   K   Q   K   Y   G   A   G   Y   H   M   T   L   V   K   E   P   H   C   N

                                                2300
CCG GAA GAC ATC TCC CAG CTG GTC CAC CAC CAC GTG CCC AAC GCC ACG CTG GAG AGC AGC GCT GGG GCC GAG CTG TCT TTC ATC CTT CCC
P   E   D   I   S   Q   L   V   H   H   H   V   P   N   A   T   L   E   S   S   A   G   A   E   L   S   F   I   L   P

                                                2400
AGA GAG AGC ACG CAC AGG TTT GAA GGT CTC TTT GCT AAA CTG GAG AAG AAG CAG AAA GAG CTG GGC ATT GCC AGC TTT GGG GCA TCC ATC
R   E   S   T   H   R   F   E   G   L   F   A   K   L   E   K   K   Q   K   E   L   G   I   A   S   F   G   A   S   I

                                                2500
ACC ACC ATG GAG GAA GTC TTC CTT CGG GTC GGG AAG CTG GTG GAC AGC AGT ATG GAC ATC CAG GCC ATC CAG CTC CCT GCC CTG CAG TAC
T   T   M   E   E   V   F   L   R   V   G   K   L   V   D   S   S   M   D   I   Q   A   I   Q   L   P   A   L   Q   Y

                                                2600
CAG CAC GAG AGG CGC GCC AGC GAC TGG GCT GTG GAC AGC AAC CTC TGT GGG GCC ATG GAC CCC TCC GAC GGC ATT GGA GCC CTC ATC GAG
Q   H   E   R   R   A   S   D   W   A   V   D   S   N   L   C   G   A   M   D   P   S   D   G   I   G   A   L   I   E

GAG GAG CGC ACC GCT GTC AAG CTC AAC ACT GGG CTC GCC CTG CAC TGC CAG CAA TTC TGG GCC ATG TTC CTG AAG AAG GCC GCA TAC AGC
E   E   R   T   A   V   K   L   N   T   G   L   A   L   H   C   Q   Q   F   W   A   M   F   L   K   K   A   A   Y   S

2700
TGG CGC GAG TGG AAA ATG GTG GCG GCA CAG GTC CTG GTG CCT CTG ACC TGC GTC ACC CTG GCC CTC CTG GCC ATC AAC TAC TCC TCG GAG
W   R   E   W   K   M   V   A   A   Q   V   L   V   P   L   T   C   V   T   L   A   L   L   A   I   N   Y   S   S   E
```

FIG. 8D

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
                2800
CTC TTC GAC GAC CCC ATG CTG AGG CTG ACC TTG GGC GAG TAC GGC AGA ACC GTC GTG CCC TTC TCA GTT CCC GGG ACC TCC CAG CTG GGT
L   F   D   D   P   M   L   R   L   T   L   G   E   Y   G   R   T   V   V   P   F   S   V   P   G   T   S   Q   L   G

                        2900
CAG CAG CTG TCA GAG CAT CTG AAA GAC GCA CTG CAG GCT GAG GGA CAG GAG CCC CGC GAG GTG CTC GGT GAC CTG GAG GAG TTC TTG ATC
Q   Q   L   S   E   H   L   K   D   A   L   Q   A   E   G   Q   E   P   R   E   V   L   G   D   L   E   E   F   L   I

                                3000
TTC AGG GCT TCT GTG GAG GGG GGC GGC TTT AAT GAG CGG TGC CTT GTG GCA GCG TCC TTC AGA GAT GTG GGA GAG CGC ACG GTC GTC AAC
F   R   A   S   V   E   G   G   G   F   N   E   R   C   L   V   A   A   S   F   R   D   V   G   E   R   T   V   V   N

                                        3100
GCC TTG TTC AAC AAC CAG GCG TAC CAC TCT CCA GCC ACT GCC CTG GCC GTC GTG GAC AAC CTT CTG TTC AAG CTG CTG TGC GGG CCT CAC
A   L   F   N   N   Q   A   Y   H   S   P   A   T   A   L   A   V   V   D   N   L   L   F   K   L   L   C   G   P   H

                                                3200
GCC TCC ATT GTG GTC TCC AAC TTC CCC CAG CCC CGG AGC GCC CTG CAG GCT GCC AAG GAC CAG TTT AAC GAG GGC CGG AAG GGA TTC GAC
A   S   I   V   V   S   N   F   P   Q   P   R   S   A   L   Q   A   A   K   D   Q   F   N   E   G   R   K   G   F   D

                                                        3300
ATT GCC CTC AAC CTG CTC TTC GCC ATG GCA TTC TTG GCC AGC ACG TTC TCC ATC CTG GCG GTC AGC GAG AGG GCC GTG CAG GCC AAG CAT
I   A   L   N   L   L   F   A   M   A   F   L   A   S   T   F   S   I   L   A   V   S   E   R   A   V   Q   A   K   H

                                                                3400
GTG CAG TTT GTG AGT GGA GTC CAC GTG GCC AGT TTC TGG CTC TCT GCT CTG CTG TGG GAC CTC ATC TCC TTC CTC ATC CCC AGT CTG CTG
V   Q   F   V   S   G   V   H   V   A   S   F   W   L   S   A   L   L   W   D   L   I   S   F   L   I   P   S   L   L
```

FIG. 8E

```
                                                                                                          3500
CTG CTG GTG GTG TTT AAG GCC TTC GAC GTG CGT GCC TTC ACG CGG GAC GGC CAC ATG GCT GAC ACC CTG CTG CTG CTC CTG CTC TAC GGC
 L   L   V   V   F   K   A   F   D   V   R   A   F   T   R   D   G   H   M   A   D   T   L   L   L   L   L   L   Y   G

TGG GCC ATC ATC CCC CTC ATG TAC CTG ATG AAC TTC TTC TTC TTG GGG GCG GCC ACT GCC TAC ACG AGG CTG ACC ATC TTC AAC ATC CTG
 W   A   I   I   P   L   M   Y   L   M   N   F   F   F   L   G   A   A   T   A   Y   T   R   L   T   I   F   N   I   L

3600
TCA GGC ATC GCC ACC TTC CTG ATG GTC ACC ATC ATG CGC ATC CCA GCT GTA AAA CTG GAA GAA CTT TCC AAA ACC CTG GAT CAC GTG TTC
 S   G   I   A   T   F   L   M   V   T   I   M   R   I   P   A   V   K   L   E   E   L   S   K   T   L   D   H   V   F

         3700
CTG GTG CTG CCC AAC CAC TGT CTG GGG ATG GCA GTC AGC AGT TTC TAC GAG AAC TAC GAG ACG CGG AGG TAC TGC ACC TCC TCC GAG GTC
 L   V   L   P   N   H   C   L   G   M   A   V   S   S   F   Y   E   N   Y   E   T   R   R   Y   C   T   S   S   E   V

                        3800
GCC GCC CAC TAC TGC AAG AAA TAT AAC ATC CAG TAC CAG GAG AAC TTC TAT GCC TGG AGC GCC CCG GGG GTC GGC CGG TTT GTG GCC TCC
 A   A   H   Y   C   K   K   Y   N   I   Q   Y   Q   E   N   F   Y   A   W   S   A   P   G   V   G   R   F   V   A   S

                                    3900
ATG GCC GCC TCA GGG TGC GCC TAC CTC ATC CTG CTC TTC CTC ATC GAG ACC AAC CTG CTT CAG AGA CTC AGG GGC ATC CTC TGC GCC CTC
 M   A   A   S   G   C   A   Y   L   I   L   L   F   L   I   E   T   N   L   L   Q   R   L   R   G   I   L   C   A   L

                                                4000
CGG AGG AGG CGG ACA CTG ACA GAA TTA TAC ACC CGG ATG CCT GTG CTT CCT GAG GAC CAA GAT GTA GCG GAC GAG AGG ACC CGC ATC CTG
 R   R   R   R   T   L   T   E   L   Y   T   R   M   P   V   L   P   E   D   Q   D   V   A   D   E   R   T   R   I   L
```

FIG. 8F

BNSDOCID: <WO__9748797A1_I_>

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
                                                                4100
GCC CCC AGC CCG GAC TCC CTG CTC CAC ACA CCT CTG ATT ATC AAG GAG CTC TCC AAG GTG TAC GAG CAG CGG GTG CCC CTC CTG GCC GTG
 A   P   S   P   D   S   L   L   H   T   P   L   I   I   K   E   L   S   K   V   Y   E   Q   R   V   P   L   L   A   V

                                                        4200
GAC AGG CTC TCC CTC GCG GTG CAG AAA GGG GAG TGC TTC GGC CTG CTG GGC TTC AAT GGA GCC GGG AAG ACC ACG ACT TTC AAA ATG CTG
 D   R   L   S   L   A   V   Q   K   G   E   C   F   G   L   L   G   F   N   G   A   G   K   T   T   T   F   K   M   L

                                                                4300
ACC GGG GAG GAG AGC CTC ACT TCT GGG GAT GCC TTT GTC GGG GGT CAC AGA ATC AGC TCT GAT GTC GGA AAG GTG CGG CAG CGG ATC GGC
 T   G   E   E   S   L   T   S   G   D   A   F   V   G   G   H   R   I   S   S   D   V   G   K   V   R   Q   R   I   G

                                                                        4400
TAC TGC CCG CAG TTT GAT GCC TTG CTG GAC CAC ATG ACA GGC CGG GAG ATG CTG GTC ATG TAC GCT CGG CTC CGG GGC ATC CCT GAG CGC
 Y   C   P   Q   F   D   A   L   L   D   H   M   T   G   R   E   M   L   V   M   Y   A   R   L   R   G   I   P   E   R

CAC ATC GGG GCC TGC GTG GAG AAC ACT CTG CGG GGC CTG CTG CTG GAG CCA CAT GCC AAC AAG CTG GTC AGG ACG TAC AGT GGT GGT AAC
 H   I   G   A   C   V   E   N   T   L   R   G   L   L   L   E   P   H   A   N   K   L   V   R   T   Y   S   G   G   N

500
AAG CGG AAG CTG AGC ACC GGC ATC GCC CTG ATC GGA GAG CCT GCT GTC ATC TTC CTG GAC GAG CCG TCC ACT GGC ATG GAC CCC GTG GCC
 K   R   K   L   S   T   G   I   A   L   I   G   E   P   A   V   I   F   L   D   E   P   S   T   G   M   D   P   V   A

                4600
CGG CGC CTG CTT TGG GAC ACC GTG GCA CGA GCC CGA GAG TCT GGC AAG GCC ATC ATC ATC ACC TCC CAC AGC ATG GAG GAG TGT GAG GCC
 R   R   L   L   W   D   T   V   A   R   A   R   E   S   G   K   A   I   I   I   T   S   H   S   M   E   E   C   E   A
```

FIG. 8G

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
                                  4700
CTG TGC ACC CGG CTG GCC ATC ATG GTG CAG GGG CAG TTC AAG TGC CTG GGC AGC CCC CAG CAC CTC AAG AGC AAG TTC GGC AGC GGC TAC
 L   C   T   R   L   A   I   M   V   Q   G   Q   F   K   C   L   G   S   P   Q   H   L   K   S   K   F   G   S   G   Y

                                  4800
TCC CTG CGG GCC AAG GTG CAG AGT GAA GGG CAA CAG GAG GCG CTG GAG GAG TTC AAG GCC TTC GTG GAC CTG ACC TTT CCA GGC AGC GTC
 S   L   R   A   K   V   Q   S   E   G   Q   Q   E   A   L   E   E   F   K   A   F   V   D   L   T   F   P   G   S   V

                                  4900
CTG GAA GAT GAG CAC CAA GGC ATG GTC CAT TAC CAC CTG CCG GGC CGT GAC CTC AGC TGG GCG AAG GTT TTC GGT ATT CTG GAG AAA GCC
 L   E   D   E   H   Q   G   M   V   H   Y   H   L   P   G   R   D   L   S   W   A   K   V   F   G   I   L   E   K   A

                                  5000
AAG GAA AAG TAC GGC GTG GAC GAC TAC TCC GTG AGC CAG ATC TCG CTG GAA CAG GTC TTC CTG AGC TTC GCC CAC CTG CAG CCG CCC ACC
 K   E   K   Y   G   V   D   D   Y   S   V   S   Q   I   S   L   E   Q   V   F   L   S   F   A   H   L   Q   P   P   T

GCA GAG GAG GGG CGA TGA GGGGTGGCGGCTGTCTCGCCATCAGGCAGGGACAGGACGGGCAAGCAGGGCCCATCTTACATCCTCTCTCTCCAAGTTTATCTCATCCTTTATTT
 A   E   E   G   R

TTAATCACTTTTTTCTATGATGGATATGAAAAATTCAAGGCAGTATGCACAGAATGGACGAGTGCAGCCCAGCCCTCATGCCCAGGATCAGCATGCGCATCTCCATGTCTGCATACTCT
GGAGTCACTTTCCCAGAGCTGGGGCAGGCCGGGCAGTCTGCGGGCAAGCTCCGGGGTCTCTGGGTGGAGAGCTGACCCAGGAAGGGCTGCAGCTGAGCTGGGGGTTGAATTTCTCCAGG
CACTCCCTGGAGAGAGGACCCAGTGACTTGTCCAAGTTTACACACGACACTAATCTCCCCTGGGGAGGAAGCGGGAAGCCAGCCAGGTTGAACTGTAGCGAGGCCCCCAGGCCGCCAGG
AATGGACCATGCAGATCACTGTCAGTGGAGGGAAGCTGCTGACTGTGATTAGGTGCTGGGGTCTTAGCGTCCAGCGCAGCCCGGGGGCATCCTGGAGGCTCTGCTCCTTAGGGCATGGT
AGTCACCGCGAAGCCGGGCACCGTCCCACAGCATCTCCTAGAAGCAGCCGGCACAGGAGGGAAGGTGGCCAGGCTCGAAGCAGTCTCTGTTTCCAGCACTGCACCCTCAGGAAGTCGCC
CGCCCCAGGACACGCAGGGACCACCCTAAGGGCTGGGTGGCTGTCTCAAGGACACATTGAATACGTTGTGACCATCCAGAAAATAAATGCTGAGGGGACACAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAA
```

FIG. 8H

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
abc1     CMEEEPTHLRLGVSIQNLVKVYRDGMK--VAVDGLALNFYEGQITSFLGHNGAGKTTTMSILTGLFPPTSGTAYILGK   989
abc2     -MEEEPTHLPLVVCVDKLTKVYKNDKK--LALNKLSLNLYENQVVSFLGHNGAGKTTTMSILTGLFPPTSGSATIYGH    90
hABC3    YFEAEPEDLVAGIKIKHLSKVFRVGNKDRAAVRDLNLNLYEGQITVLLGHNGAGKTTTLSMLTGLFPPTSGRAYISGY   575
           * **  *    . .  * **.:   *   *. * ** **.*.   **********.*.**********  * * *

abc1     DIRSEMSSIRQNLGVCPQHNVLFDMLTVEEHIWFYARLKGLSEKHVKAEMEQMALDVGLPPSKLKSKTSQLSGGMQRK  1067
abc2     DIRTEMDEIRKNLGMCPQHNVLFDRLTVEEHLWFYSRLKSMAQEEIRKETDKMIEDLELS-NKRHSLVQTLSGGMKRK   167
hABC3    EISQDMVQIRKSLGLCPQHDILFDNLTVAEHLYFYAQLKGLSRQKCPEEVKQMLHIIGLE-DKWNSRSRFLSGGMRRK   652
           *  .*  **. **.**** .*** *** ** .**..**  ..      *  .*   .  *  *  *    *****.**

abc1     LSVALAFVGGSKVVILDEPTAGVDPYSRRGIWELLLKYRQGRTIILSTHHMDEADILGDRIAIISHGKLCCVGSSLFL  1145
abc2     LSVAIAFVGGSRAIILDEPTAGVDPYARRAIWDLILKYKPGRTILLSTHHMDEADLLGDRIAIISHGKLKCCGSPLFL   245
hABC3    LSIGIALIAGSKVLILDEPTSGMDAISRRAIWDLLQRQKSDRTIVLTTHFMDEADLLGDRIAIMAKGELQCCGSSLFL   538
         **. .*. **. .******.*.*  .** **.*. . .  ***.*.** *****.*******..* * * ** ***

abc1     KNQLGTGYYLTLVKKDVESSLSSCRNSSSTVSCLKKEDSVSQSSSDAGLGSDHESDTLTIDVSAISNLIRKHVSEARL  1223
abc2     KGAYXDGYRLTLVKQPAEPGTSQEPGLASSPSGCPRLSSCSEPQ-------------------VSQFIRKHVASSLL   303
hABC3    KQKYGAGYHMTLVKEPHCNPED-----------------------------------------ISQLVHHHVPNATL   766
         *     **  .****                                                .*. ...**   . *

abc1     VEDIGHELTYVLPYEAAKEGAFVELFHEIDDRLSDLGISSYGISETTLEEIFLKVAEE------SGVDAETSDG-TLP  1294
abc2     VSDTSTELSYILPSEAVKKGAFERLFQQLEHSLDALHLSSFGLMDTTLEEVFLKVSEEDQSLENSEADVKESRKDVLP   380
hABC3    ESSAGAELSFILPRESTHR--FEGLFAKLEKKQKELGIASFGASITTMEEVFLRVGKLVD----SSMDIQAIQLPALQ   838
               **...** *. .   *  **  ..      * ..*.*   **.**.**.*         *  *        *
```

FIG. 9A

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
abc1    ARRNRRAFG-------------DKQSCLHPFTEDDAVDPND----SDIDPESR-ETDLLSGMD---------------  1339
abc2    GAEGLTAVGGQAGNLARCSELAQSQASLQSASSVGSARGEEGTGYSDGYGDYRPLFDNLQDPDNVSLQEAEMEALAQV   459
hABC3   YQHERRASD-----------------WAVDSNLCGAMDPSD--GIGALIEEER-----------------------   872

abc1    GKGSYQLKGWKLTQQQFVALLWKRLLIARRSRKGFFAQIVLPAVFVCIALVFSLIVPPFGKYPSLELQPWMYNEQYTF  1417
abc2    GQGSRKLEGWWLKMRQFHGLLVKRFHCARRNSKALCSQILLPAFFVCVAMTVALSVPEIGDLPPLVLSPSQYHNYTQP   537
hABC3   -TAVKLNTGLALHCQQFWAMFLKKAAYSWREWKMVAAQVLVPLTCVTLALLAINYSSELFDDPMLRLTLGEYGRTVVP   949

abc1    VSNDAP-------------EDMGTQELLNALTKDPGFGTRCMEGNP-----IPDTPCLAGEE-----DWTISPVPQS  1471
abc2    RGNFIPYANEERQEYRLRLSPDASPQQLVSTFRLPSGVGATCVLKSPANGSLGPMLNLSSGESRLLAARFFDSMCLES   615
hABC3   FS--VP-----------------GTSQLGQQLS-------------------------------------EHLK   967

abc1    IVDLFQNGNWTMKNPSPACQCS-----SDKIKKMLPVCPPGAGGLPPPQRKQKTADILQNLTGRNISDYLVKTYVQIIA  1545
abc2    FTQGLPLSNFVPPPPSPAPSDSPVXPDEDSLQAWNMSLPPTAG--PETWTSAPSLPRLVHEPVRCTCSAQGTGFSCPSS   692
hABC3   DALQAE-------------------------GQE-------------PREVLGDLEEFLIFRASVEGGGFNERCLVA  1006

abc1    KS-LKNKIWVNEFRYGGFSLGVSNSQALPPSHEVNDAIKQMKKLLKLTKDTSADRFLSSLGRFMAGLDTKNNVKVWFNN  1623
abc2    VGGHPPQMRVVTGDILTDITGHNVSEYLLFTSDRFRLHRYGAITFGNVQKSIPASFGARVPPMVRKIAVRRVAQVLYNN   771
hABC3   AS-----------------------------------------------------------FRDVGERTVVNALFNN  1024

abc1    KGWHAISSFLNVINNAILRANLQKGE-NPSQYGITAFNHPLNLTKQQLSEVALMTTSVDVLVSICVIFAMSFVPASFVV  1701
abc2    KGYHSMPTYLNSLNNAILRANLPKSKGNPAAYXITVTNHPMNKTSASLSLDYLLQG-TDVVIAIFIIVAMSFVPASFVV   849
hABC3   QAYHSPATALAVVDNLLFKLLCGPHA------SIVVSNFPQPRSALQAAKDQFNEGRKGFDIALNLLFAMAFLASTFSI  1097
```

FIG. 9B

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
abc1    FLIQERVSKAKHLQFISGVKPVIYWLSNFVWDMCNYVVPATLVIIIFICFQQKSYVSSTNLPVLALLLLLYGWSITPLM  1780
abc2    FLVAEKSTKAKHLQFVSGCNPVIYWLANYVWDMLNYLVPATCCVIILFVFDLPAYTSPTNFPAVLSLFLLYGWSITPIM   928
hABC3   LAVSERAVQAKHVQFVSGVHVASFWLSALLWDLISFLIPSLLLLVVFKAFDVRAFTRDGHMADTLLLLLLYGWAIIPLM  1176
           . *.  .*** ** **     .**.  .**.  ...*.  ...   *  ..     .        * ***** * * .*

abc1    YPASFVFKIPSTAYVVLTSVNLFIGINGSVATFVLELFTNNK-LNDINDILKSVFLIFPHFCLGRGLIDMVKN-------  1852
abc2    YPASFWFEVPSSAYVFLIVINLFIGITATVATFLLQLFEHDKDLKVVNSYLKSCFLIFPNYNLGHGLMEMAYN-------  1001
hABC3    YLMNFFFLGAATAYTRLTIFNILSGIATFLMVTIMRIPAVKL--EELSKTLDHVFLVLPNHCLGMAVSSFYENYETRRYC  1254
        *   * *    ..**  *   *.  **    .  . . .        .  *   **. *.  **   .      *

abc1     --QAMADALERFGE-NRFVSPLSWDL--VGRNLFAMAVEGVVFFLITVLIQYRFFIRPR-------------PVKAKLP  1913
abc2     --EYINEYYAKIGQFDKMKSPFEWDI--VTRGLVAMTVEGFVGFFLTIMCQYNFLRQPQ-------------RLPVSTK  1063
hABC3     TSSEVAAHYCKKYNIQYQENFYAWSAPGVGRFVASMAASGCAYLILLFLIETNLLQRLRGILCALRRRRTLTELYTRMP  1333
             .  .                 *   * * . .*.  *   .  .  .  .  .  .                .

abc1     PLNDEDEDVRRERQRILDGGGQ---NDILEIKELTKIYRRK---RKPAVDRICIGIP-PGECFGLLGVNGAGKSTTFKM  1985
abc2     PVED-DVDVASERQRVLRGDAD---NDMVKIENLTKVYKSRKIGRILAVDRLCLGVCVPGECFGLLGVNGAGKTSTFKM  1138
hABC3    VLPE-DQDVADERTRILAPSPDSLLHTPLIIKELSKVYEQR--VPLLAVDRLSLAVQ-KGECFGLLGFNGAGKTTTFKM  1408
          . . * **  ** * .*          .  . *  *.*.*  .       ****... .   ******** ***** ..****

abc1    LTGDTPVTRGDAFLNKNSILSNIHEVHQNMGYCPQFDAITELLTGREHVEFFALLRGVPEKEVGKFGEWAIRKLGLVKY  2064
abc2    LTGDESTTGGEAFVNGHSVLKDLLQVQQSLGYCPQFDVPVDELTAREHLQLYTRLRCIPWKDEAQVVKWALEKLELTKY  1217
hABC3   LTGEESLTSGDAFVGGHRISSDVGKVRQRIGYCPQFDALLDHMTGREMLVMYARLRGIPERHIGACVENTLRGLLLEPH  1487
        ***.   * *.**.. . .   .  *.* .*******   . .* ** . .. ** .* .          ..  * *
```

FIG. 9C

BNSDOCID: <WO__9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
abc1     GEKYASNYSGGNKRKLSTAMALIGGPPVVFLDEPTTGMDPKARRFLWNCALSIVKEGRSVVLTSHSMEECEALCTRMAI 2143
abc2     ADKPAGTYSGGNKRKLSTAIALIGYPAFIFLDEPTTGMDPKARRFLWNLILDLIKTGRSVVLTSHSMEECEALCTRLAI 1296
hABC3    ANKLVRTYSGGNKRKLSTGIALIGEPAVIFLDEPSTGMDPVARRLLWDTVARARESGKAIIITSHSMEECEALCTRLAI 1566
           *    .***********  .**** *   .***** .***** *** **          *.....***************.**

abc1     MVNGRFRCLGSVQHLKNRFGDGYTIVVRIAGSNP--DLKPVQEFFGLAFPGSVLKEKHRNMLQYQLPSSLSSLARIFSI 2220
abc2     MVNGRLHCLGSIQHLKNRFGDGYMITVRTKSSQ---NVKDVVRFFNRNFPEAHAQGKTPYKVQYQLKSEHISLAQVFSK 1372
hABC3    MVQGQFKCLGSPQHLKSKFGSGYXLRAKVQSEGQQEALEEFKAFVDLTFPGSVLEDEHQGMVHYHLPGRDLSWAKVFGI 1645
         **.*. .**** **** .** **  .  .          .    *    **          . * *    * * .*

abc1     LSQSKKRLHIEDYSVSQTTLDQVFVNFAKDQSDDD-----------HLKDLSLHKN-QTVVDVAVLTS---------- 2276
abc2     MEQVVGVLGIEDYSVSQTTLDNVFVNFAKKQSDNVEQQEAEPSSLPSPLGLLSLLRPRPAPTELRALVADEPEDLDTED 1451
hABC3    LEKAKEKYGVDDYSVSQISLEQVFLSFAHLQPPTAEEGR------------------------------------- 1684
               ..******  *..**. **

abc1     ----FLQDEKVKESYV-----  2288
abc2     EGLISFEEERAQLSFNTDTLC  1472
hABC3    ----------------------
```

FIG. 9D

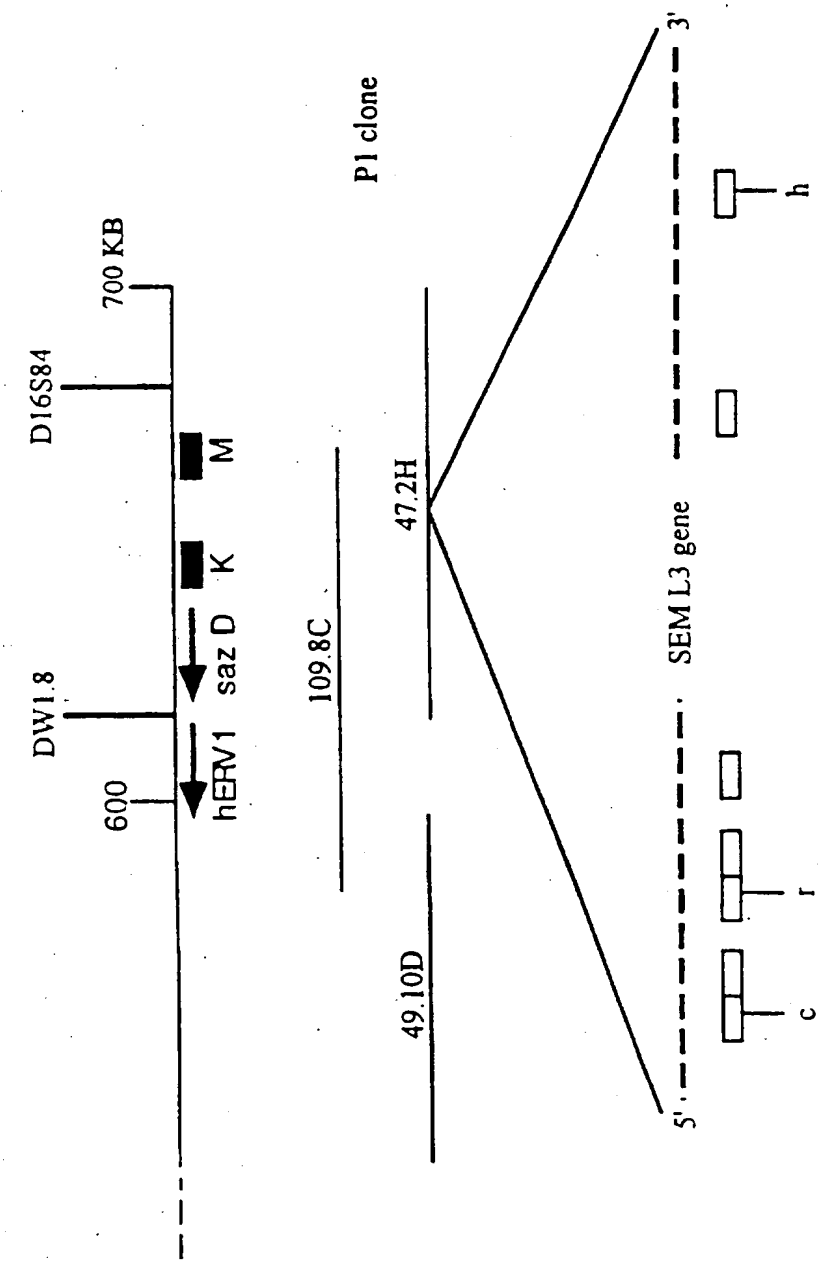

FIG. 10

BNSDOCID: <WO___9748797A1_I_>

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
GGCGGCTAGCGGCGAGGCCCCTTCCTGTACCTTCAGGGATCGGCCACCATGTCCCACCGGAAGTTTTCCGCCCCTCGGCACGGACACCTGGGCTTCCTGC  100
                                                  M  S  H  R  K  F  S  A  P  R  H  G  H  L  G  F  L    17

CCCATAAGAGGAGCCACCGGCACCGGGGCAAGGTGAAGACGTGGCCGCGGGATGACCCCAGCCAGCCCGTGCACCTCACGGCCTTCCTGGGCTACAAGGC  200
P  H  K  R  S  H  R  H  R  G  K  V  K  T  W  P  R  D  D  P  S  Q  P  V  H  L  T  A  F  L  G  Y  K  A    51

GGGCATGACCCACACCCTGCGGGAGGTGCACCGGCCGGGGCTCAAAATTTCCAAACGGGAGGAGGTGGAGGCGGTGACAATTGTAGAAACGCCGCCCCTA  300
  G  M  T  H  T  L  R  E  V  H  R  P  G  L  K  I  S  K  R  E  E  V  E  A  V  T  I  V  E  T  P  P  L    84

GTGGTGGTGGGCGTGGTGGGCTACGTGGCCACCCCTCGAGGTCTCCGGAGCTTCAAGACCATCTTTGCAGAACACCTCAGTGATGAGTGCCGGCGCCGAT  400
 V  V  V  G  V  V  G  Y  V  A  T  P  R  G  L  R  S  F  K  T  I  F  A  E  H  L  S  D  E  C  R  R  R    117

TCTACAAGGACTGGCACAAGAGCAAGAAGAAAGCCTTCACCAAGGCCTGCAAGAGGTGGCGGGACACAGACGGGAAAAAGCAGCTACAGAAGGACTTCGC  500
F  Y  K  D  W  H  K  S  K  K  K  A  F  T  K  A  C  K  R  W  R  D  T  D  G  K  K  Q  L  Q  K  D  F  A  151

CGCCATGAAGAAGTACTGCAAGGTCATTCGGGTCATTGTCCACACTCAGATGAAACTGCTGCCCTTCCGGCAGAAGAAGGCCCACATCATGGAGATCCAG  600
  A  M  K  K  Y  C  K  V  I  R  V  I  V  H  T  Q  M  K  L  L  P  F  R  Q  K  K  A  H  I  M  E  I  Q  184

CTGAACGGTGGCACGGTGGCCGAGAAGGTGGCCTGGGCCCAGGCCCGGCTGGAGAAGCAGGTGCCCGTGCACAGCGTGTTCAGCCAGAGTGAGGTCATTG  700
 L  N  G  G  T  V  A  E  K  V  A  W  A  Q  A  R  L  E  K  Q  V  P  V  H  S  V  F  S  Q  S  E  V  I    217

ATGTCATTGCTGTCACCAAGGGTCGAGGCGTCAAAGGGGTCACAAGCCGCTGGCATACCAAGAAGCTGCCGCGGAAGACCCATAAGGGCCTGCGCAAGGT  800
D  V  I  A  V  T  K  G  R  G  V  K  G  V  T  S  R  W  H  T  K  K  L  P  R  K  T  H  K  G  L  R  K  V  251
```

FIG. 11A

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

```
GGCCTGCATTGGCGCCTGGCACCCCGCCCGCGTGGGCTGCTCCATTGCTCGGGCCGGGCAGAAGGGCTATCACCACCGCACGGAGCTCAACAAGAAGATC  900
  A  C  I  G  A  W  H  P  A  R  V  G  C  S  I  A  R  A  G  Q  K  G  Y  H  H  R  T  E  L  N  K  K  I   284

TTCCGCATCGGCAGGGGCCCGCACATGGAGGACGGGAAGCTGGTGAAGAACAATGCATCCACCAGCTACGACGTGACTGCCAAGTCCATCACACCGCTGG 1000
  F  R  I  G  R  G  P  H  M  E  D  G  K  L  V  K  N  N  A  S  T  S  Y  D  V  T  A  K  S  I  T  P  L   317

GTGGCTTCCCCCACTACGGGGAAGTGAACAACGACTTCGTCATGCTGAAGGGTTGTATTGCTGGTACCAAGAAGCGGGTCATTACGCTGAGAAAGTCCCT 1100
G  G  F  P  H  Y  G  E  V  N  N  D  F  V  M  L  K  G  C  I  A  G  T  K  K  R  V  I  T  L  R  K  S  L  351

CCTGGTGCATCACAGTCGCCAAGCCGTGGAGAATATTGAGCTCAAGTTCATTGACACCACCTCCAAGTTCGGCCATGGCCGCTTCCAGACAGCCCAAGAG 1200
  L  V  H  H  S  R  Q  A  V  E  N  I  E  L  K  F  I  D  T  T  S  K  F  G  H  G  R  F  Q  T  A  Q  E   384

AAGAGGGCCTTCATGGGCCCCCAAAAGAAGCATCTGGAGAAGGAAACGCCGGAGACCTCGGGAGACTTGTAGGCTGTGTGGGGTGGATGAACCCTGAAGC 1300
  K  R  A  F  M  G  P  Q  K  K  H  L  E  K  E  T  P  E  T  S  G  D  L  *                              407

GCACCGCACTGTCTGCCCCAATGTCTAACAAAGGCCGGAGGCGACTCTTCCTGCGAGGTCTCAGAGCGCTGTGTAACCGCCCAAGGGGTTCACCTTGCCT 1400

GCTGCCTAGACAAAGCCGATTCATTAAGACAGGGGAATTGCAATAGAGAAAGAGTAATTCACACAGAGCTGGCTGTGCGGGAGACCGGAGTTTTATGTTT 1500

TATTATTACTCAAATCGATCTCTTTGAGCAAAAAAAAAAAAAAAAAA                                                       1548
```

FIG. 11B

```
HUMAN L3    MSHRKFSAPRHGSLGFLPRKRSSRHRGKVKSFPKDDPSKPVHLTAFLGYK
BOVINE L3   ----------------------------------S-----------
MURINE L3   ----------------------------------A-----------
SEM L3      ----------H-----H---H-------TW-R----Q----------

HUMAN L3    AGMTHIVREVDRPGSKVNKKEVVEAVTIVETPPMVVVGIVGYVETPRGLR
BOVINE L3   --------------------------------I-------------
MURINE L3   ------------------------------------------------
SEM L3      -----TL---H---L-IS-R-E----------L----V----A------

HUMAN L3    TFKTVFAEHISDECKRRFYKNWHKSKKKAFTKYCKKWQDEDGKKQLEKDF
BOVINE L3   ----I-------------------------------A-------R--
MURINE L3   ----------------------------------DT---------
SEM L3      S---I----L----R-----D----------A--R-R-T------Q---

HUMAN L3    SSMKKYCQVIRVIAHTQMRLLPLRQKKAHLMEIQVNGGTVAEKLDWARER
BOVINE L3   --------------------------------V-----------------
MURINE L3   N----------I------------------------------------
SEM L3      AA-----K-----V----K---F------I----L--------VA--QA-

HUMAN L3    LEQQVPVNQVFGQDEMIDVIGVTKGKGYKGVTSRWHTKKLPRKTHRGLRK
BOVINE L3   ------------------------------------------------
MURINE L3   -------S----------------------------------------
SEM L3      --K----HS--S-S-V----A----R-V----------------K----

HUMAN L3    VACIGAWHPARVAFSVARAGQKGYHHRTEINKKIYKIGQGYLIKDGKLIK
BOVINE L3   ------------------------------------------------
MURINE L3   --------------T---------------------------------
SEM L3      ------------GC-I-------------L----FR--R-PHME----V-

HUMAN L3    NNASTDYDLSDKSINPLGGFVHYGEVTNDFVMLKGCVVGTKKRVLTLRKS
BOVINE L3   ------------------------------------------------
MURINE L3   --------------------------------I---------------
SEM L3      -----S--VTA---T-----P-----N---------IA-----I-----

HUMAN L3    LLVQTKRRALEKIDLKFIDTTSKFGHGRFQTMEEKKAFMGPLKKDRIAKE
BOVINE L3   -----------------------------V-----------------
MURINE L3   ------------------------------------------------
SEM L3      ---HHS-Q-V-N-E----------------AQ--R-----Q--HLEKET

HUMAN L3    EGA----
BOVINE L3   -------
MURINE L3   -------
SEM L3      PETSGDL
```

FIG. 12

BNSDOCID: <WO___9748797A1_I_>

SUBSTITUTE SHEET (RULE 26)

BNSDOCID: <WO___9748797A1_I_>

```
          10          20          30          40          50          60          70
CGG GAC ACC AAG TTT AGG GAG GAC TGC CCG CCG GAT CGC GAG GAA CTG GGC CGC CAC AGC TGG GCT GTC CTC
 R   D   T   K   F   R   E   D   C   P   P   D   R   E   E   L   G   R   H   S   W   A   V   L

      80          90          100         110         120         130         140
CAC ACC CTG GCC GCC TAC TAC CCC GAC CTG CCC ACC CCA GAA CAG CAG CAA GAC ATG GCC CAG TTC ATA CAT
 H   T   L   A   A   Y   Y   P   D   L   P   T   P   E   Q   Q   Q   D   M   A   Q   F   I   H

  150         160         170         180         190         200         210
TTA TTT TCT AAG TTT TAC CCC TGT GAG GAG TGT GCT GAA GAC CTA AGA AAA AGG CTG TGC AGG AAC CAC CCA
 L   F   S   K   F   Y   P   C   E   E   C   A   E   D   L   R   K   R   L   C   R   N   H   P

  220         230         240         250         260         270         280
GAC ACC CGC ACC CGG GCA TGC TTC ACA CAG TGG CTG TGC CAC CTG CAC AAT GAA GTG AAC CGC AAG CTG GGC
 D   T   R   T   R   A   C   F   T   Q   W   L   C   H   L   H   N   E   V   N   R   K   L   G

290         300         310         320         330         340         350         360
AAG CCT GAC TTC GAC TGC TCA AAA GTG GAT GAG CGC TGG CGC GAC GGC TGG AAG GAT GGC TCC TGT GAC TAG
 K   P   D   F   D   C   S   K   V   D   E   R   W   R   D   G   W   K   D   G   S   C   D

      370         380         390         400         410         420         430         440
AGGGT GGTCA GCCAG AGCTC ATGGG ACAGC TAGCC AGGCA TGGTT GGATA GGGGC AGGGC ACTCA TTAAA GTGCA TCACA

      450         460
GCCAG AAAAA AAAAA AAAAA AAAAA AAA
```

FIG. 13

```
rALR     1 MRTQQKRDIKFREDCPQDREELGRNTWAFLHTLAAYYPDMPTPEQQQDMAQFIHIFSKFY
hALR       ------RDTKFREDCPPDREELGRHSWAVLHTLAAYYPDLPTPEQQQDMAQFIHLFSKFY
                 ** ******** ******** .. ** ********** ********************* *****

rALR    61 PCEECAEDIRKRIDRSQPDTSTRVSFSQWLCRLHNEVNRKLGKPDFDCSRVDERWRDGWK
hALR       PCEECAEDLRKRLCRNHPDTRTRACFTQWLCHLHNEVNRKLGKPDFDCSKVDERWRDGWK
           ********** *** . *** ** * . ***** ********************** **********

rALR   121 DGSCD
hALR       DGSCD
           *****
```

FIG. 14

BNSDOCID: <WO___9748797A1_I_>

FIGURE 15A

```
CACATAAAAT ACACCGCCCC GGCGCCCAGG CTCGGTGCTG GAGAGTCATG CCTGTGAGCC      60

CTGGGCACCT CCTGATGTCC TGCGAGGTCA CGGTGTTCCC AAACCTCAGG GTTGCCCTGC     120

CCCACTCCAG AGGCTCTCAG GCCCCACCCC GGAGCCCTCT GTGCGGAGCC GCCTCCTCCT     180

GGCCAGTTCC CCAGTAGTCC TGAAGGGAGA CCTGCTGTGT GGAGCCTCTT CTGGGACCCA     240

GCCATGAGTG TGGAGCTGAG CAACTGAACC TGAAACTCTT CCACTGTGAG TCAAGGAGGC     300

TTTTCCGCAC ATGAAGGACG CTGAGCGGGA AGGACTCCTC TCTGCCTGCA GTTGTAGCGA     360

GTGGACCAGC ACCAGGGGCT CTCTAGACTG CCCCTCCTCC ATCGCCTTCC CTGCCTCTCC     420

AGGACAGAGC AGCCACGTCT GCACACCTCG CCCTCTTTAC ACTCAGTTTT CAGAGCACGT     480

TTCTCCTATT TCCTGCGGGT TGCAGCGCCT ACTTGAACTT ACTCAGACCA CCTACTTCTC     540

TAGCAGCACT GGGCGTCCCT TTCAGCAAGA CG ATG GCT GTG CTC AGG CAG CTG       593
                                       Met Ala Val Leu Arg Gln Leu
                                         1               5

GCG CTC CTC CTC TGG AAG AAC TAC ACC CTG CAG AAG CGG AAG GTC CTG       641
Ala Leu Leu Leu Trp Lys Asn Tyr Thr Leu Gln Lys Arg Lys Val Leu
        10                  15                  20

GTG ACG GTC CTG GAA CTC TTC CTG CCA TTG CTG TTT TCT GGG ATC CTC       689
Val Thr Val Leu Glu Leu Phe Leu Pro Leu Leu Phe Ser Gly Ile Leu
    25                  30                  35

ATC TGG CTC CGC TTG AAG ATT CAG TCG GAA AAT GTG CCC AAC GCC ACC       737
Ile Trp Leu Arg Leu Lys Ile Gln Ser Glu Asn Val Pro Asn Ala Thr
40                  45                  50                  55

ATC TAC CCG GGC CAG TCC ATC CAG GAG CTG CCT CTG TTC TTC ACC TTC       785
Ile Tyr Pro Gly Gln Ser Ile Gln Glu Leu Pro Leu Phe Phe Thr Phe
                60                  65                  70

CCT CCG CCA GGA GAC ACC TGG GAG CTT GCC TAC ATC CCT TCT CAC AGT       833
Pro Pro Pro Gly Asp Thr Trp Glu Leu Ala Tyr Ile Pro Ser His Ser
            75                  80                  85

GAC GCT GCC AAG GCC GTC ACT GAG ACA GTG CGC AGG GCA CTT GTG ATC       881
Asp Ala Ala Lys Ala Val Thr Glu Thr Val Arg Arg Ala Leu Val Ile
        90                  95                  100

AAC ATG CGA GTG CGC GGC TTT CCC TCC GAG AAG GAC TTT GAG GAC TAC       929
Asn Met Arg Val Arg Gly Phe Pro Ser Glu Lys Asp Phe Glu Asp Tyr
    105                 110                 115
```


BNSDOCID: <WO___9748797A1_I_>

FIGURE 15B

```
ATT AGG TAC GAC AAC TGC TCG TCC AGC GTG CTG GCC GCC GTG GTC TTC      977
Ile Arg Tyr Asp Asn Cys Ser Ser Ser Val Leu Ala Ala Val Val Phe
120                 125                 130                 135

GAG CAC CCC TTC AAC CAC AGC AAG GAG CCC CTG CCG CTG GCG GTG AAA     1025
Glu His Pro Phe Asn His Ser Lys Glu Pro Leu Pro Leu Ala Val Lys
                140                 145                 150

TAT CAC CTA CGG TTC AGT TAC ACA CGG AGA AAT TAC ATG TGG ACC CAA     1073
Tyr His Leu Arg Phe Ser Tyr Thr Arg Arg Asn Tyr Met Trp Thr Gln
            155                 160                 165

ACA GGC TCC TTT TTC CTG AAA GAG ACA GAA GGC TGG CAC ACT ACT TCC     1121
Thr Gly Ser Phe Phe Leu Lys Glu Thr Glu Gly Trp His Thr Thr Ser
        170                 175                 180

CTT TTC CCG CTT TTC CCA AAC CCA GGA CCA AGG GAA CTA ACA TCC CCT     1169
Leu Phe Pro Leu Phe Pro Asn Pro Gly Pro Arg Glu Leu Thr Ser Pro
    185                 190                 195

GAT GGC GGA GAA CCT GGG TAC ATC CGG GAA GGC TTC CTG GCC GTG CAG     1217
Asp Gly Gly Glu Pro Gly Tyr Ile Arg Glu Gly Phe Leu Ala Val Gln
200                 205                 210                 215

CAT GCT GTG GAC CGG GCC ATC ATG GAG TAC CAT GCC GAT GCC GCC ACA     1265
His Ala Val Asp Arg Ala Ile Met Glu Tyr His Ala Asp Ala Ala Thr
                220                 225                 230

CGC CAG CTG TTC CAG AGA CTG ACG GTG ACC ATC AAG AGG TTC CCG TAC     1313
Arg Gln Leu Phe Gln Arg Leu Thr Val Thr Ile Lys Arg Phe Pro Tyr
            235                 240                 245

CCG CCG TTC ATC GCA GAC CCC TTC CTC GTG GCC ATC CAG TAC CAG CTG     1361
Pro Pro Phe Ile Ala Asp Pro Phe Leu Val Ala Ile Gln Tyr Gln Leu
        250                 255                 260

CCC CTG CTG CTG CTG CTC AGC TTC ACC TAC ACC GCG CTC ACC ATT GCC     1409
Pro Leu Leu Leu Leu Leu Ser Phe Thr Tyr Thr Ala Leu Thr Ile Ala
    265                 270                 275

CGT GCT GTC GTG CAG GAG AAG GAA AGG AGG CTG AAG GAG TAC ATG CGC     1457
Arg Ala Val Val Gln Glu Lys Glu Arg Arg Leu Lys Glu Tyr Met Arg
280                 285                 290                 295

ATG ATG GGG CTC AGC AGC TGG CTG CAC TGG AGT GCC TGG TTC CTC TTG     1505
Met Met Gly Leu Ser Ser Trp Leu His Trp Ser Ala Trp Phe Leu Leu
                300                 305                 310

TTC TTC CTC TTC CTC CTC ATC GCC GCC TCC TTC ATG ACC CTG CTC TTC     1553
Phe Phe Leu Phe Leu Leu Ile Ala Ala Ser Phe Met Thr Leu Leu Phe
            315                 320                 325
```


BNSDOCID: <WO___9748797A1_I_>

FIGURE 15C

```
TGT GTC AAG GTG AAG CCA AAT GTA GCC GTG CTG TCC CGC AGC GAC CCC      1601
Cys Val Lys Val Lys Pro Asn Val Ala Val Leu Ser Arg Ser Asp Pro
        330                 335                 340

TCC CTG GTG CTC GCC TTC CTG CTG TGC TTC GCC ATC TCT ACC ATC TCC      1649
Ser Leu Val Leu Ala Phe Leu Leu Cys Phe Ala Ile Ser Thr Ile Ser
    345                 350                 355

TTC AGC TTC ATG GTC AGC ACC TTC TTC AGC AAA GCC AAC ATG GCA GCA      1697
Phe Ser Phe Met Val Ser Thr Phe Phe Ser Lys Ala Asn Met Ala Ala
360                 365                 370                 375

GCC TTC GGA GGC TTC CTC TAC TTC TTC ACC TAC ATC CCC TAC TTC TTC      1745
Ala Phe Gly Gly Phe Leu Tyr Phe Phe Thr Tyr Ile Pro Tyr Phe Phe
                380                 385                 390

GTG GCC CCT CGG TAC AAC TGG ATG ACT CTG AGC CAG AAG CTC TGC TCC      1793
Val Ala Pro Arg Tyr Asn Trp Met Thr Leu Ser Gln Lys Leu Cys Ser
            395                 400                 405

TGC CTC CTG TCT AAT GTC GCC ATG GCA ATG GGA GCC CAG CTC ATT GGG      1841
Cys Leu Leu Ser Asn Val Ala Met Ala Met Gly Ala Gln Leu Ile Gly
        410                 415                 420

AAA TTT GAG GCG AAA GGC ATG GGC ATC CAG TGG CGA GAC CTC CTG AGT      1889
Lys Phe Glu Ala Lys Gly Met Gly Ile Gln Trp Arg Asp Leu Leu Ser
    425                 430                 435

CCC GTC AAC GTG GAC GAC GAC TTC TGC TTC GGG CAG GTG CTG GGG ATG      1937
Pro Val Asn Val Asp Asp Asp Phe Cys Phe Gly Gln Val Leu Gly Met
440                 445                 450                 455

CTG CTG CTG GAC TCT GTG CTC TAT GGC CTG GTG ACC TGG TAC ATG GAG      1985
Leu Leu Leu Asp Ser Val Leu Tyr Gly Leu Val Thr Trp Tyr Met Glu
                460                 465                 470

GCC GTC TTC CCA GGG CAG TTC GGC GTG CCT CAG CCC TGG TAC TTC TTC      2033
Ala Val Phe Pro Gly Gln Phe Gly Val Pro Gln Pro Trp Tyr Phe Phe
            475                 480                 485

ATC ATG CCC TCC TAT TGG TGT GGG AAG CCA AGG GCG GTT GCA GGG AAG      2081
Ile Met Pro Ser Tyr Trp Cys Gly Lys Pro Arg Ala Val Ala Gly Lys
        490                 495                 500

GAG GAA GAA GAC AGT GAC CCC GAG AAA GCA CTC AGA AAC GAG TAC TTT      2129
Glu Glu Glu Asp Ser Asp Pro Glu Lys Ala Leu Arg Asn Glu Tyr Phe
    505                 510                 515

GAA GCC GAG CCA GAG GAC CTG GTG GCG GGG ATC AAG ATC AAG CAC CTG      2177
Glu Ala Glu Pro Glu Asp Leu Val Ala Gly Ile Lys Ile Lys His Leu
520                 525                 530                 535
```


BNSDOCID: <WO___9748797A1_I_>

FIGURE 15D

```
TCC AAG GTG TTC AGG GTG GGA AAT AAG GAC AGG GCG GCC GTC AGA GAC      2225
Ser Lys Val Phe Arg Val Gly Asn Lys Asp Arg Ala Ala Val Arg Asp
                540                 545                 550

CTG AAC CTC AAC CTG TAC GAG GGA CAG ATC ACC GTC CTG CTG GGC CAC      2273
Leu Asn Leu Asn Leu Tyr Glu Gly Gln Ile Thr Val Leu Leu Gly His
            555                 560                 565

AAC GGT GCC GGG AAG ACC ACC ACC CTC TCC ATG CTC ACA GGT CTC TTT      2321
Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Met Leu Thr Gly Leu Phe
        570                 575                 580

CCC CCC ACC AGT GGA CGG GCA TAC ATC AGC GGG TAT GAA ATT TCC CAG      2369
Pro Pro Thr Ser Gly Arg Ala Tyr Ile Ser Gly Tyr Glu Ile Ser Gln
    585                 590                 595

GAC ATG GTT CAG ATC CGG AAG AGC CTG GGC CTG TGC CCG CAG CAC GAC      2417
Asp Met Val Gln Ile Arg Lys Ser Leu Gly Leu Cys Pro Gln His Asp
600                 605                 610                 615

ATC CTG TTT GAC AAC TTG ACA GTC GCA GAG CAC CTT TAT TTC TAC GCC      2465
Ile Leu Phe Asp Asn Leu Thr Val Ala Glu His Leu Tyr Phe Tyr Ala
                620                 625                 630

CAG CTG AAG GGC CTG TCA CGT CAG AAG TGC CCT GAA GAA GTC AAG CAG      2513
Gln Leu Lys Gly Leu Ser Arg Gln Lys Cys Pro Glu Glu Val Lys Gln
            635                 640                 645

ATG CTG CAC ATC ATC GGC CTG GAG GAC AAG TGG AAC TCA CGG AGC CGC      2561
Met Leu His Ile Ile Gly Leu Glu Asp Lys Trp Asn Ser Arg Ser Arg
        650                 655                 660

TTC CTG AGC GGG GGC ATG AGG CGC AAG CTC TCC ATC GGC ATC GCC CTC      2609
Phe Leu Ser Gly Gly Met Arg Arg Lys Leu Ser Ile Gly Ile Ala Leu
    665                 670                 675

ATC GCA GGC TCC AAG GTG CTG ATA CTG GAC GAG CCC ACC TCG GGC ATG      2657
Ile Ala Gly Ser Lys Val Leu Ile Leu Asp Glu Pro Thr Ser Gly Met
680                 685                 690                 695

GAC GCC ATC TCC AGG AGG GCC ATC TGG GAT CTT CTT CAG CGG CAG AAA      2705
Asp Ala Ile Ser Arg Arg Ala Ile Trp Asp Leu Leu Gln Arg Gln Lys
                700                 705                 710

AGT GAC CGC ACC ATC GTG CTG ACC ACC CAC TTC ATG GAC GAG GCT GAC      2753
Ser Asp Arg Thr Ile Val Leu Thr Thr His Phe Met Asp Glu Ala Asp
            715                 720                 725

CTG CTG GGA GAC CGC ATC GCC ATC ATG GCC AAG GGG GAG CTG CAG TGC      2801
Leu Leu Gly Asp Arg Ile Ala Ile Met Ala Lys Gly Glu Leu Gln Cys
        730                 735                 740
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BNSDOCID: <WO___9748797A1_I_>

FIGURE 15E

```
TGC GGG TCC TCG CTG TTC CTC AAG CAG AAA TAC GGT GCC GGC TAT CAC      2849
Cys Gly Ser Ser Leu Phe Leu Lys Gln Lys Tyr Gly Ala Gly Tyr His
    745                 750                 755

ATG ACG CTG GTG AAG GAG CCG CAC TGC AAC CCG GAA GAC ATC TCC CAG      2897
Met Thr Leu Val Lys Glu Pro His Cys Asn Pro Glu Asp Ile Ser Gln
760                 765                 770                 775

CTG GTC CAC CAC CAC GTG CCC AAC GCC ACG CTG GAG AGC AGC GCT GGG      2945
Leu Val His His His Val Pro Asn Ala Thr Leu Glu Ser Ser Ala Gly
                780                 785                 790

GCC GAG CTG TCT TTC ATC CTT CCC AGA GAG AGC ACG CAC AGG TTT GAA      2993
Ala Glu Leu Ser Phe Ile Leu Pro Arg Glu Ser Thr His Arg Phe Glu
            795                 800                 805

GGT CTC TTT GCT AAA CTG GAG AAG AAG CAG AAA GAG CTG GGC ATT GCC      3041
Gly Leu Phe Ala Lys Leu Glu Lys Lys Gln Lys Glu Leu Gly Ile Ala
        810                 815                 820

AGC TTT GGG GCA TCC ATC ACC ACC ATG GAG GAA GTC TTC CTT CGG GTC      3089
Ser Phe Gly Ala Ser Ile Thr Thr Met Glu Glu Val Phe Leu Arg Val
    825                 830                 835

GGG AAG CTG GTG GAC AGC AGT ATG GAC ATC CAG GCC ATC CAG CTC CCT      3137
Gly Lys Leu Val Asp Ser Ser Met Asp Ile Gln Ala Ile Gln Leu Pro
840                 845                 850                 855

GCC CTG CAG TAC CAG CAC GAG AGG CGC GCC AGC GAC TGG GCT GTG GAC      3185
Ala Leu Gln Tyr Gln His Glu Arg Arg Ala Ser Asp Trp Ala Val Asp
                860                 865                 870

AGC AAC CTC TGT GGG GCC ATG GAC CCC TCC GAC GGC ATT GGA GCC CTC      3233
Ser Asn Leu Cys Gly Ala Met Asp Pro Ser Asp Gly Ile Gly Ala Leu
            875                 880                 885

ATC GAG GAG GAG CGC ACC GCT GTC AAG CTC AAC ACT GGG CTC GCC CTG      3281
Ile Glu Glu Glu Arg Thr Ala Val Lys Leu Asn Thr Gly Leu Ala Leu
        890                 895                 900

CAC TGC CAG CAA TTC TGG GCC ATG TTC CTG AAG AAG GCC GCA TAC AGC      3329
His Cys Gln Gln Phe Trp Ala Met Phe Leu Lys Lys Ala Ala Tyr Ser
    905                 910                 915

TGG CGC GAG TGG AAA ATG GTG GCG GCA CAG GTC CTG GTG CCT CTG ACC      3377
Trp Arg Glu Trp Lys Met Val Ala Ala Gln Val Leu Val Pro Leu Thr
920                 925                 930                 935

TGC GTC ACC CTG GCC CTC CTG GCC ATC AAC TAC TCC TCG GAG CTC TTC      3425
Cys Val Thr Leu Ala Leu Leu Ala Ile Asn Tyr Ser Ser Glu Leu Phe
                940                 945                 950
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BNSDOCID: <WO___9748797A1_I_>

FIGURE 15F

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GAC GAC CCC ATG CTG AGG CTG ACC TTG GGC GAG TAC GGC AGA ACC GTC      3473
Asp Asp Pro Met Leu Arg Leu Thr Leu Gly Glu Tyr Gly Arg Thr Val
            955                 960                 965

GTG CCC TTC TCA GTT CCC GGG ACC TCC CAG CTG GGT CAG CAG CTG TCA      3521
Val Pro Phe Ser Val Pro Gly Thr Ser Gln Leu Gly Gln Gln Leu Ser
        970                 975                 980

GAG CAT CTG AAA GAC GCA CTG CAG GCT GAG GGA CAG GAG CCC CGC GAG      3569
Glu His Leu Lys Asp Ala Leu Gln Ala Glu Gly Gln Glu Pro Arg Glu
    985                 990                 995

GTG CTC GGT GAC CTG GAG GAG TTC TTG ATC TTC AGG GCT TCT GTG GAG      3617
Val Leu Gly Asp Leu Glu Glu Phe Leu Ile Phe Arg Ala Ser Val Glu
1000                1005                1010                1015

GGG GGC GGC TTT AAT GAG CGG TGC CTT GTG GCA GCG TCC TTC AGA GAT      3665
Gly Gly Gly Phe Asn Glu Arg Cys Leu Val Ala Ala Ser Phe Arg Asp
                1020                1025                1030

GTG GGA GAG CGC ACG GTC GTC AAC GCC TTG TTC AAC AAC CAG GCG TAC      3713
Val Gly Glu Arg Thr Val Val Asn Ala Leu Phe Asn Asn Gln Ala Tyr
            1035                1040                1045

CAC TCT CCA GCC ACT GCC CTG GCC GTC GTG GAC AAC CTT CTG TTC AAG      3761
His Ser Pro Ala Thr Ala Leu Ala Val Val Asp Asn Leu Leu Phe Lys
        1050                1055                1060

CTG CTG TGC GGG CCT CAC GCC TCC ATT GTG GTC TCC AAC TTC CCC CAG      3809
Leu Leu Cys Gly Pro His Ala Ser Ile Val Val Ser Asn Phe Pro Gln
    1065                1070                1075

CCC CGG AGC GCC CTG CAG GCT GCC AAG GAC CAG TTT AAC GAG GGC CGG      3857
Pro Arg Ser Ala Leu Gln Ala Ala Lys Asp Gln Phe Asn Glu Gly Arg
1080                1085                1090                1095

AAG GGA TTC GAC ATT GCC CTC AAC CTG CTC TTC GCC ATG GCA TTC TTG      3905
Lys Gly Phe Asp Ile Ala Leu Asn Leu Leu Phe Ala Met Ala Phe Leu
                1100                1105                1110

GCC AGC ACG TTC TCC ATC CTG GCG GTC AGC GAG AGG GCC GTG CAG GCC      3953
Ala Ser Thr Phe Ser Ile Leu Ala Val Ser Glu Arg Ala Val Gln Ala
            1115                1120                1125

AAG CAT GTG CAG TTT GTG AGT GGA GTC CAC GTG GCC AGT TTC TGG CTC      4001
Lys His Val Gln Phe Val Ser Gly Val His Val Ala Ser Phe Trp Leu
        1130                1135                1140

TCT GCT CTG CTG TGG GAC CTC ATC TCC TTC CTC ATC CCC AGT CTG CTG      4049
Ser Ala Leu Leu Trp Asp Leu Ile Ser Phe Leu Ile Pro Ser Leu Leu
    1145                1150                1155
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BNSDOCID: <WO___9748797A1_I_>

FIGURE 15G

```
CTG CTG GTG GTG TTT AAG GCC TTC GAC GTG CGT GCC TTC ACG CGG GAC      4097
Leu Leu Val Val Phe Lys Ala Phe Asp Val Arg Ala Phe Thr Arg Asp
1160                1165                1170                1175

GGC CAC ATG GCT GAC ACC CTG CTG CTG CTC CTG CTC TAC GGC TGG GCC      4145
Gly His Met Ala Asp Thr Leu Leu Leu Leu Leu Leu Tyr Gly Trp Ala
                    1180                1185                1190

ATC ATC CCC CTC ATG TAC CTG ATG AAC TTC TTC TTC TTG GGG GCG GCC      4193
Ile Ile Pro Leu Met Tyr Leu Met Asn Phe Phe Phe Leu Gly Ala Ala
            1195                1200                1205

ACT GCC TAC ACG AGG CTG ACC ATC TTC AAC ATC CTG TCA GGC ATC GCC      4241
Thr Ala Tyr Thr Arg Leu Thr Ile Phe Asn Ile Leu Ser Gly Ile Ala
        1210                1215                1220

ACC TTC CTG ATG GTC ACC ATC ATG CGC ATC CCA GCT GTA AAA CTG GAA      4289
Thr Phe Leu Met Val Thr Ile Met Arg Ile Pro Ala Val Lys Leu Glu
    1225                1230                1235

GAA CTT TCC AAA ACC CTG GAT CAC GTG TTC CTG GTG CTG CCC AAC CAC      4337
Glu Leu Ser Lys Thr Leu Asp His Val Phe Leu Val Leu Pro Asn His
1240                1245                1250                1255

TGT CTG GGG ATG GCA GTC AGC AGT TTC TAC GAG AAC TAC GAG ACG CGG      4385
Cys Leu Gly Met Ala Val Ser Ser Phe Tyr Glu Asn Tyr Glu Thr Arg
                1260                1265                1270

AGG TAC TGC ACC TCC TCC GAG GTC GCC GCC CAC TAC TGC AAG AAA TAT      4433
Arg Tyr Cys Thr Ser Ser Glu Val Ala Ala His Tyr Cys Lys Lys Tyr
            1275                1280                1285

AAC ATC CAG TAC CAG GAG AAC TTC TAT GCC TGG AGC GCC CCG GGG GTC      4481
Asn Ile Gln Tyr Gln Glu Asn Phe Tyr Ala Trp Ser Ala Pro Gly Val
        1290                1295                1300

GGC CGG TTT GTG GCC TCC ATG GCC GCC TCA GGG TGC GCC TAC CTC ATC      4529
Gly Arg Phe Val Ala Ser Met Ala Ala Ser Gly Cys Ala Tyr Leu Ile
    1305                1310                1315

CTG CTC TTC CTC ATC GAG ACC AAC CTG CTT CAG AGA CTC AGG GGC ATC      4577
Leu Leu Phe Leu Ile Glu Thr Asn Leu Leu Gln Arg Leu Arg Gly Ile
1320                1325                1330                1335

CTC TGC GCC CTC CGG AGG AGG CGG ACA CTG ACA GAA TTA TAC ACC CGG      4625
Leu Cys Ala Leu Arg Arg Arg Arg Thr Leu Thr Glu Leu Tyr Thr Arg
                1340                1345                1350

ATG CCT GTG CTT CCT GAG GAC CAA GAT GTA GCG GAC GAG AGG ACC CGC      4673
Met Pro Val Leu Pro Glu Asp Gln Asp Val Ala Asp Glu Arg Thr Arg
            1355                1360                1365
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FIGURE 15H

```
ATC CTG GCC CCC AGC CCG GAC TCC CTG CTC CAC ACA CCT CTG ATT ATC      4721
Ile Leu Ala Pro Ser Pro Asp Ser Leu Leu His Thr Pro Leu Ile Ile
        1370                1375                1380

AAG GAG CTC TCC AAG GTG TAC GAG CAG CGG GTG CCC CTC CTG GCC GTG      4769
Lys Glu Leu Ser Lys Val Tyr Glu Gln Arg Val Pro Leu Leu Ala Val
    1385                1390                1395

GAC AGG CTC TCC CTC GCG GTG CAG AAA GGG GAG TGC TTC GGC CTG CTG      4817
Asp Arg Leu Ser Leu Ala Val Gln Lys Gly Glu Cys Phe Gly Leu Leu
1400                1405                1410                1415

GGC TTC AAT GGA GCC GGG AAG ACC ACG ACT TTC AAA ATG CTG ACC GGG      4865
Gly Phe Asn Gly Ala Gly Lys Thr Thr Thr Phe Lys Met Leu Thr Gly
                1420                1425                1430

GAG GAG AGC CTC ACT TCT GGG GAT GCC TTT GTC GGG GGT CAC AGA ATC      4913
Glu Glu Ser Leu Thr Ser Gly Asp Ala Phe Val Gly Gly His Arg Ile
            1435                1440                1445

AGC TCT GAT GTC GGA AAG GTG CGG CAG CGG ATC GGC TAC TGC CCG CAG      4961
Ser Ser Asp Val Gly Lys Val Arg Gln Arg Ile Gly Tyr Cys Pro Gln
        1450                1455                1460

TTT GAT GCC TTG CTG GAC CAC ATG ACA GGC CGG GAG ATG CTG GTC ATG      5009
Phe Asp Ala Leu Leu Asp His Met Thr Gly Arg Glu Met Leu Val Met
    1465                1470                1475

TAC GCT CGG CTC CGG GGC ATC CCT GAG CGC CAC ATC GGG GCC TGC GTG      5057
Tyr Ala Arg Leu Arg Gly Ile Pro Glu Arg His Ile Gly Ala Cys Val
1480                1485                1490                1495

GAG AAC ACT CTG CGG GGC CTG CTG CTG GAG CCA CAT GCC AAC AAG CTG      5105
Glu Asn Thr Leu Arg Gly Leu Leu Leu Glu Pro His Ala Asn Lys Leu
                1500                1505                1510

GTC AGG ACG TAC AGT GGT GGT AAC AAG CGG AAG CTG AGC ACC GGC ATC      5153
Val Arg Thr Tyr Ser Gly Gly Asn Lys Arg Lys Leu Ser Thr Gly Ile
            1515                1520                1525

GCC CTG ATC GGA GAG CCT GCT GTC ATC TTC CTG GAC GAG CCG TCC ACT      5201
Ala Leu Ile Gly Glu Pro Ala Val Ile Phe Leu Asp Glu Pro Ser Thr
        1530                1535                1540

GGC ATG GAC CCC GTG GCC CGG CGC CTG CTT TGG GAC ACC GTG GCA CGA      5249
Gly Met Asp Pro Val Ala Arg Arg Leu Leu Trp Asp Thr Val Ala Arg
    1545                1550                1555

GCC CGA GAG TCT GGC AAG GCC ATC ATC ATC ACC TCC CAC AGC ATG GAG      5297
Ala Arg Glu Ser Gly Lys Ala Ile Ile Ile Thr Ser His Ser Met Glu
1560                1565                1570                1575
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BNSDOCID: <WO___9748797A1_I_>

FIGURE 15I

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GAG TGT GAG GCC CTG TGC ACC CGG CTG GCC ATC ATG GTG CAG GGG CAG      5345
Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile Met Val Gln Gly Gln
                1580                1585                1590

TTC AAG TGC CTG GGC AGC CCC CAG CAC CTC AAG AGC AAG TTC GGC AGC      5393
Phe Lys Cys Leu Gly Ser Pro Gln His Leu Lys Ser Lys Phe Gly Ser
            1595                1600                1605

GGC TAC TCC CTG CGG GCC AAG GTG CAG AGT GAA GGG CAA CAG GAG GCG      5441
Gly Tyr Ser Leu Arg Ala Lys Val Gln Ser Glu Gly Gln Gln Glu Ala
        1610                1615                1620

CTG GAG GAG TTC AAG GCC TTC GTG GAC CTG ACC TTT CCA GGC AGC GTC      5489
Leu Glu Glu Phe Lys Ala Phe Val Asp Leu Thr Phe Pro Gly Ser Val
    1625                1630                1635

CTG GAA GAT GAG CAC CAA GGC ATG GTC CAT TAC CAC CTG CCG GGC CGT      5537
Leu Glu Asp Glu His Gln Gly Met Val His Tyr His Leu Pro Gly Arg
1640                1645                1650                1655

GAC CTC AGC TGG GCG AAG GTT TTC GGT ATT CTG GAG AAA GCC AAG GAA      5585
Asp Leu Ser Trp Ala Lys Val Phe Gly Ile Leu Glu Lys Ala Lys Glu
                1660                1665                1670

AAG TAC GGC GTG GAC GAC TAC TCC GTG AGC CAG ATC TCG CTG GAA CAG      5633
Lys Tyr Gly Val Asp Asp Tyr Ser Val Ser Gln Ile Ser Leu Glu Gln
            1675                1680                1685

GTC TTC CTG AGC TTC GCC CAC CTG CAG CCG CCC ACC GCA GAG GAG GGG      5681
Val Phe Leu Ser Phe Ala His Leu Gln Pro Pro Thr Ala Glu Glu Gly
        1690                1695                1700

CGA TGAGGGGTGG CGGCTGTCTC GCCATCAGGC AGGGACAGGA CGGGCAAGCA           5734
Arg

GGGCCCATCT TACATCCTCT CTCTCCAAGT TTATCTCATC CTTTATTTTT AATCACTTTT    5794

TTCTATGATG GATATGAAAA ATTCAAGGCA GTATGCACAG AATGGACGAG TGCAGCCCAG    5854

CCCTCATGCC CAGGATCAGC ATGCGCATCT CCATGTCTGC ATACTCTGGA GTTCACTTTC    5914

CCAGAGCTGG GGCAGGCCGG GCAGTCTGCG GGCAAGCTCC GGGGTCTCTG GGTGGAGAGC    5974

TGACCCAGGA AGGGCTGCAG CTGAGCTGGG GGTTGAATTT CTCCAGGCAC TCCCTGGAGA    6034

GAGGACCCAG TGACTTGTCC AAGTTTACAC ACGACACTAA TCTCCCCTGG GGAGGAAGCG    6094

GGAAGCCAGC CAGGTTGAAC TGTAGCGAGG CCCCCAGGCC GCCAGGAATG GACCATGCAG    6154

ATCACTGTCA GTGGAGGGAA GCTGCTGACT GTGATTAGGT GCTGGGGTCT TAGCGTCCAG    6214
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BNSDOCID: <WO___9748797A1_I_>

FIGURE 15J

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CGCAGCCCGG GGGCATCCTG GAGGCTCTGC TCCTTAGGGC ATGGTAGTCA CCGCGAAGCC   6274

GGGCACCGTC CCACAGCATC TCCTAGAAGC AGCCGGCACA GGAGGGAAGG TGGCCAGGCT   6334

CGAAGCAGTC TCTGTTTCCA GCACTGCACC CTCAGGAAGT CGCCCCGCCCC AGGACACGCA   6394

GGGACCACCC TAAGGGCTGG GTGGCTGTCT CAAGGACACA TTGAATACGT TGTGACCATC   6454

CAGAAAATAA ATGCTGAGGG GACACAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA   6514

AAAAAAAAAA A                                                        6525
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BNSDOCID: <WO___9748797A1_I_>

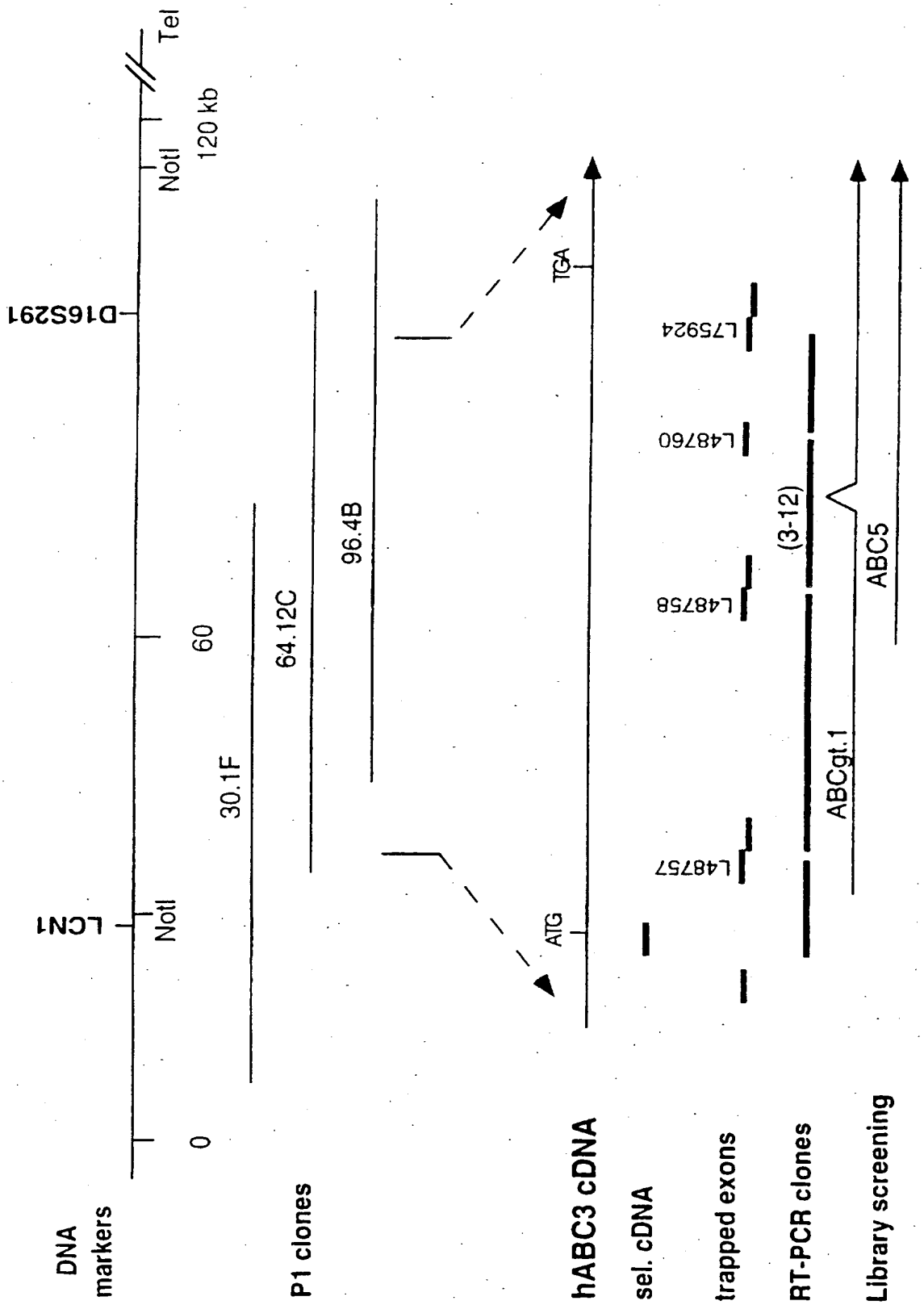


FIG. 16

BNSDOCID: <WO___9748797A1_I_>

FIG. 17A

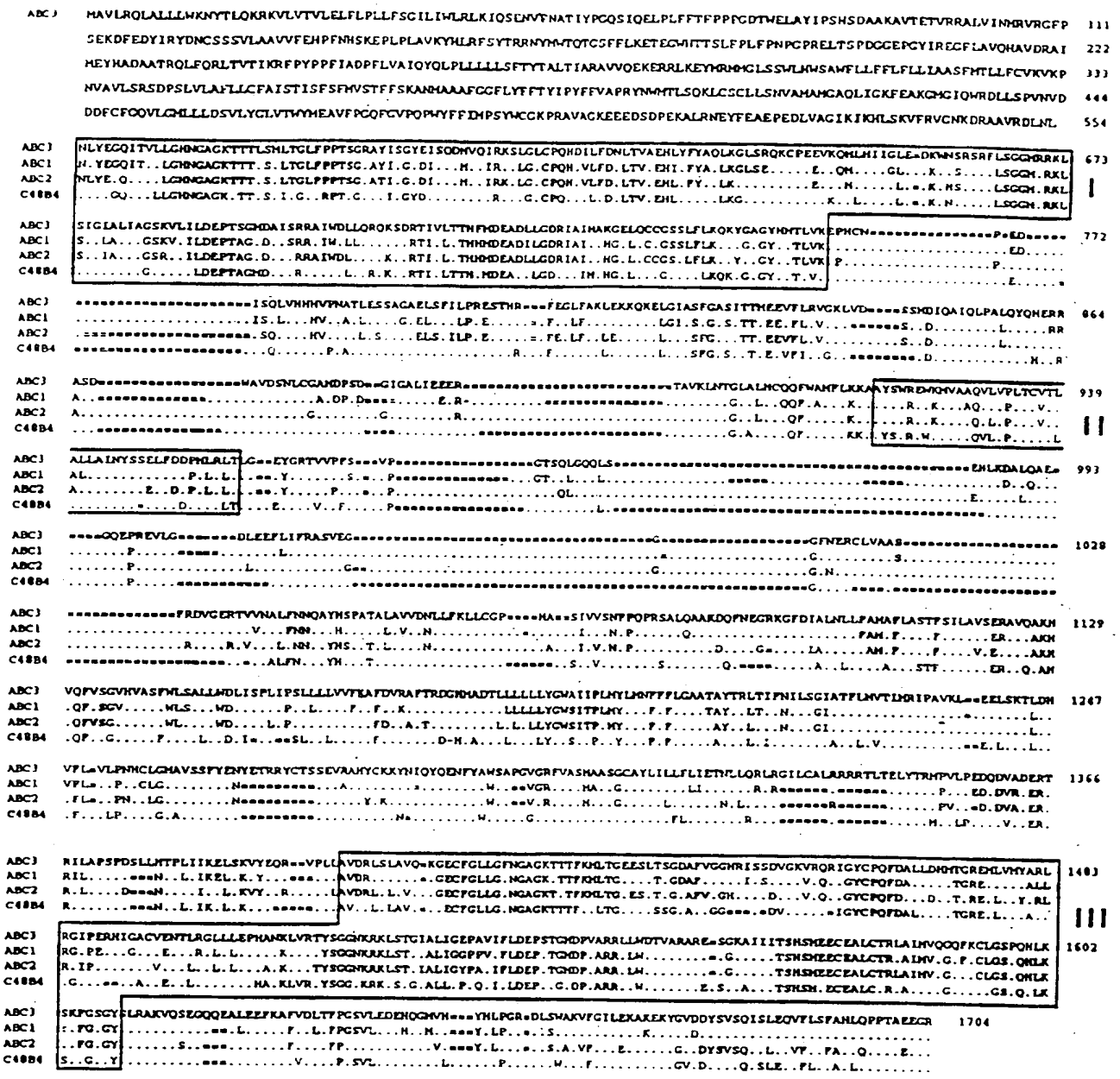
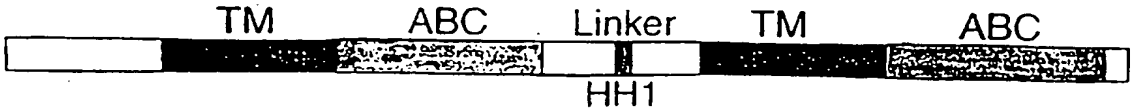


FIG. 17B



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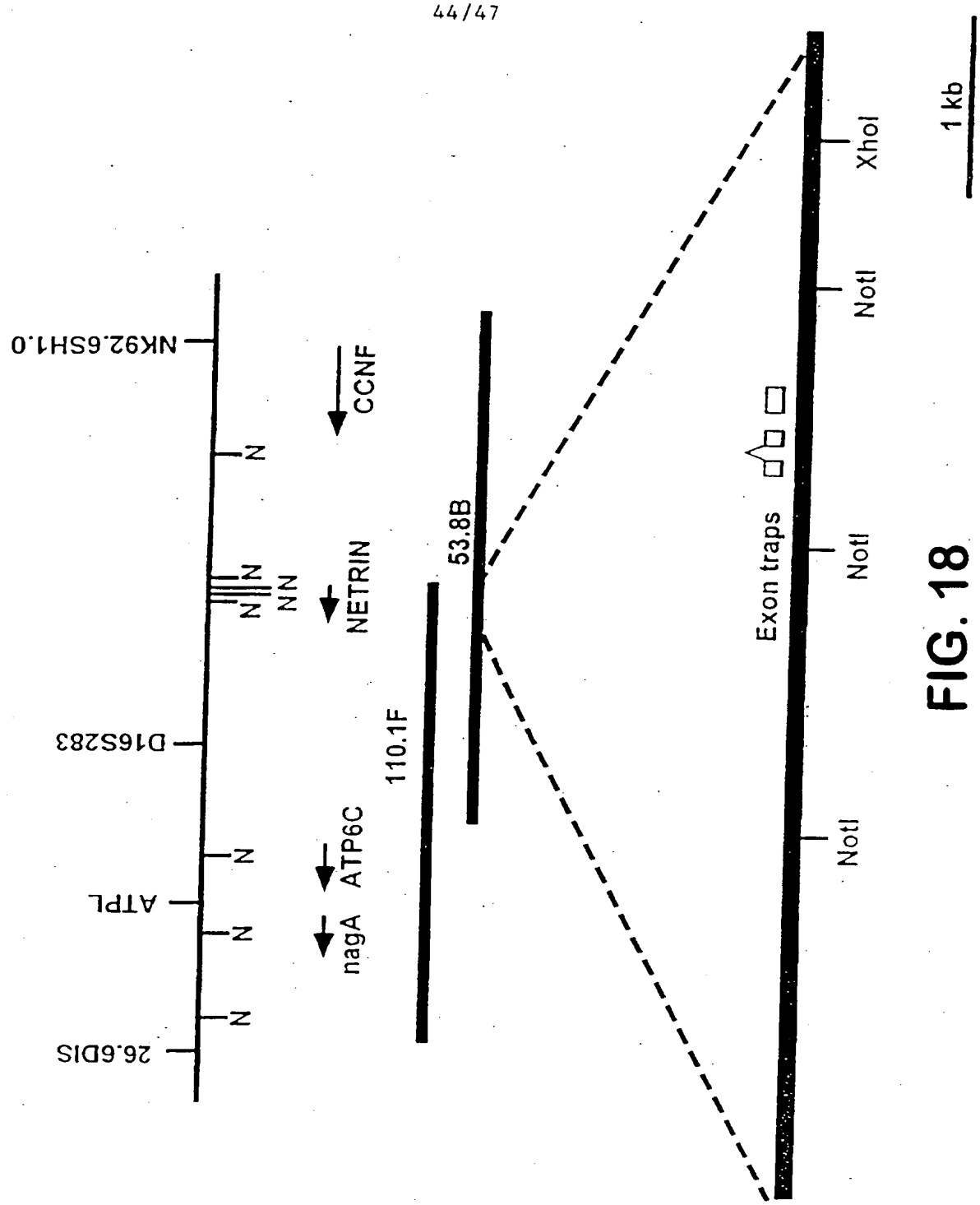

FIG. 18

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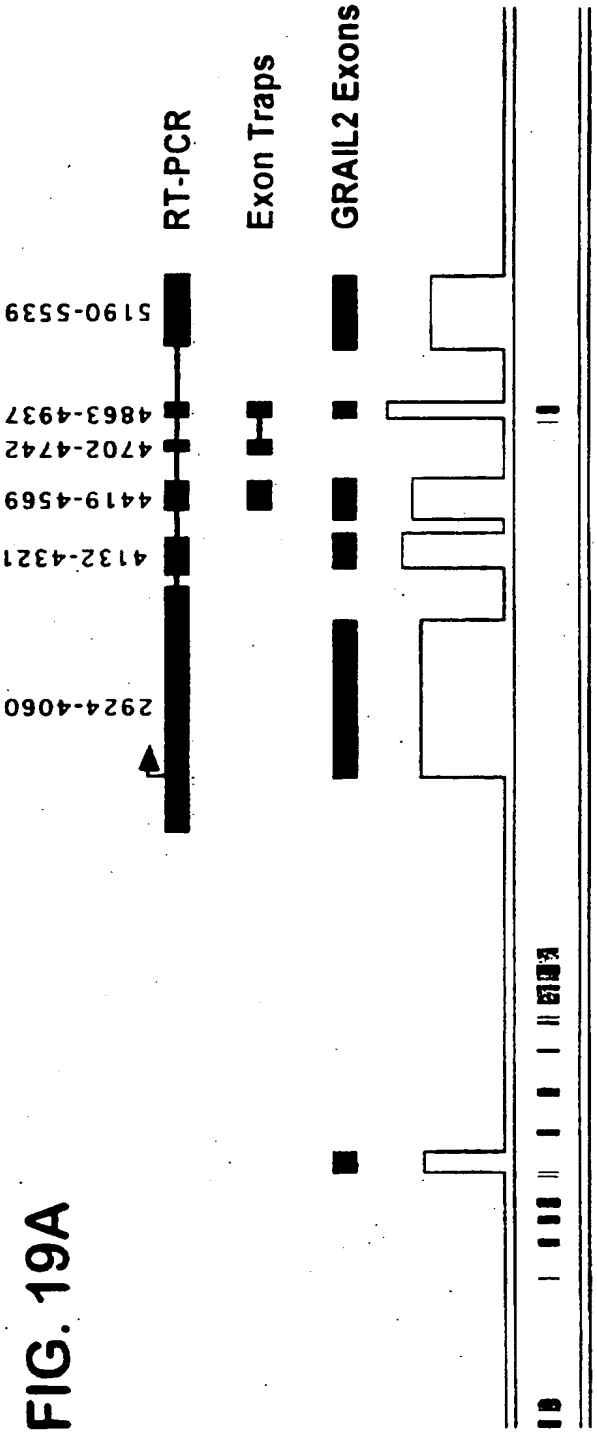


FIG. 19A

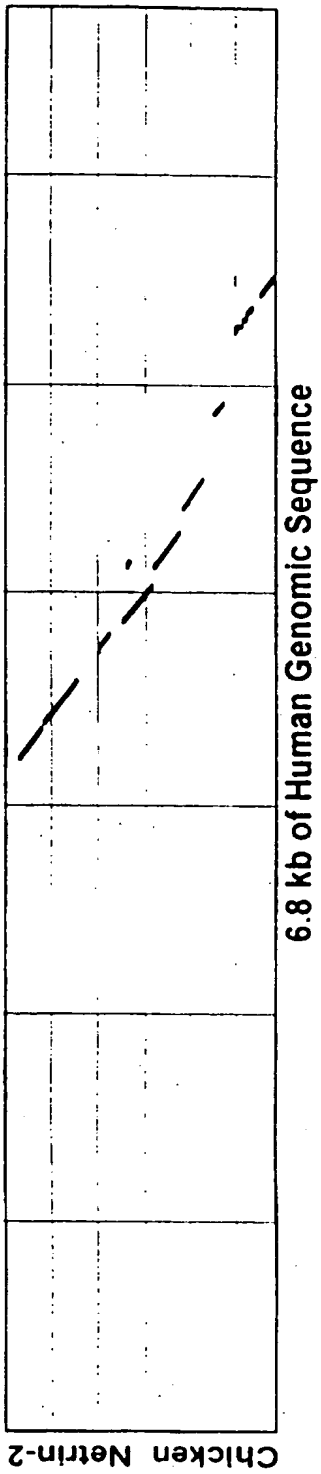


FIG. 19B

BNSDOCID: <WO___9748797A1_I_>

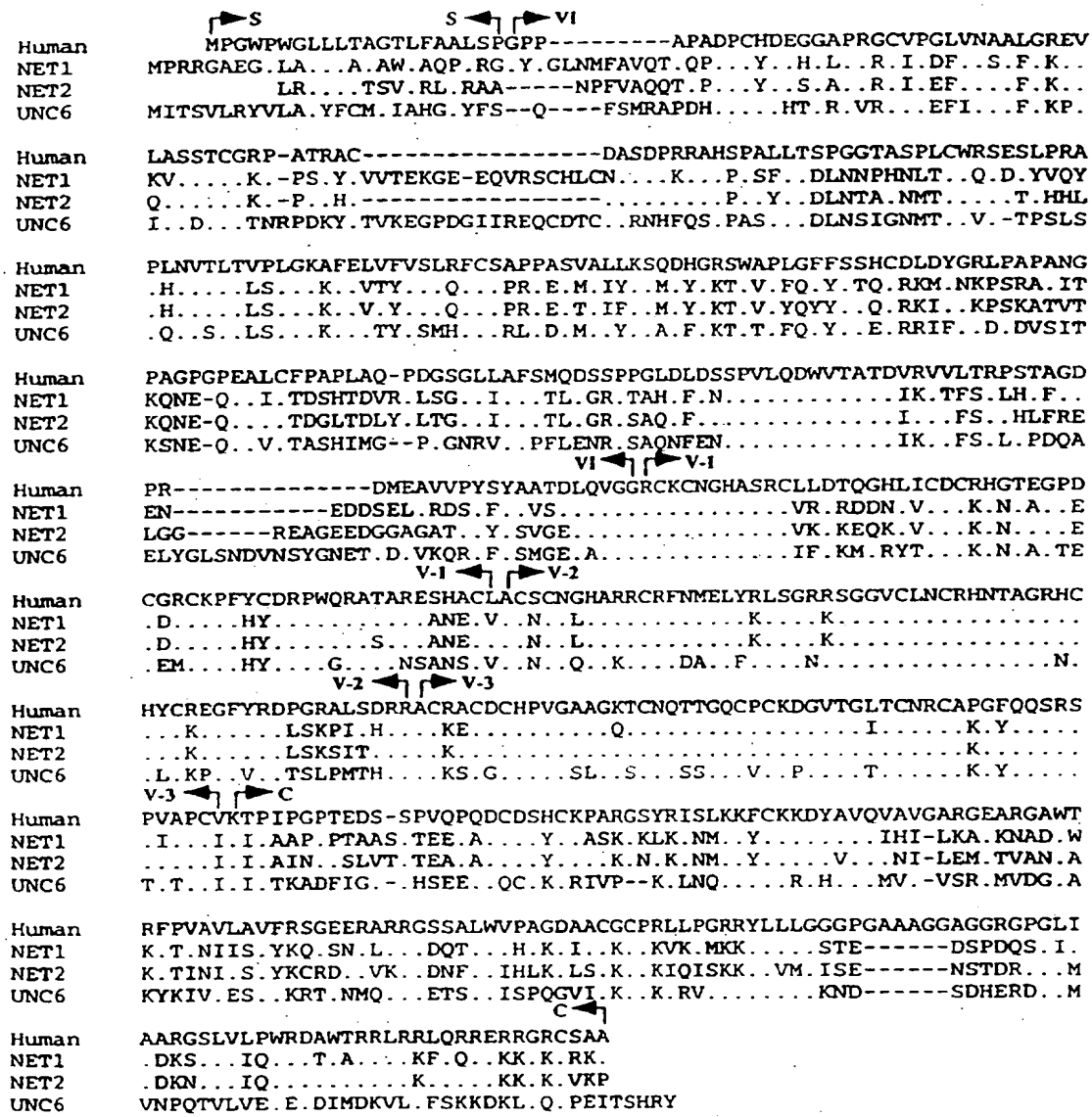
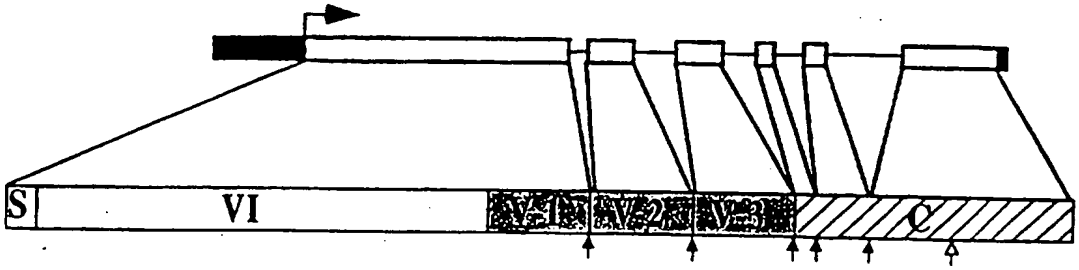


FIG. 20A

BNSDOCID: <WO___9748797A1_I_>



DOMAIN	Identity with hNet		
	Netrin-1	Netrin-2	UNC-6
VI	45.7% (106/232)	49.1% (114/232)	38.8% (90/232)
V	78.7% (133/169)	82.2% (139/169)	66.3% (112/169)
C	41.9% (67/160)	42.5% (68/160)	29.4% (47/160)
Overall	53.9% (313/580)	56.3% (327/580)	43.4% (252/580)

FIG. 20B

BNSDOCID: <WO___9748797A1_I_>

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/US 97/00785

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12N15/85 C07K14/47 C07K14/475 C07K16/18
A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 97 02346 A (GENZYME CORP) 23 January 1997 see the whole document ---	1-29
A	CELL, vol. 81, 19 May 1995, CELL PRESS,CAMBRIDGE,MA,US;, pages 471-474, XP002017866 J. DODD AND A. SCHUCHARDT: "Axon guidance: A compelling case for repelling growth clones" see the whole document ---	1-29
A	WO 95 13367 A (UNIV CALIFORNIA ;UNIV COLUMBIA (US)) 18 May 1995 see the whole document --- -/--	1-29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 1997	26. 08. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	HORNIG H.

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C.(Continuation) DOCUMENTS C[illegible]ERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CELL, vol. 78, 12 August 1994, CELL PRESS,CAMBRIDGE,MA,US;, pages 409-424, XP002017867 T. SERAFINI ET AL.: "The netrins define a family of axon outgrowth-promoting proteins homologous to C. elegans UNC-6" see the whole document ---	1-29
A	CELL, vol. 78, 12 August 1994, CELL PRESS,CAMBRIDGE,MA,US;, pages 425-435, XP002017868 T.E. KENNEDY ET AL.: "Netrins are diffusible chemotropic factors for comissural axons in the embryonic spinal cord" see the whole document ---	1-29
A	HUMAN MOLECULAR GENETICS, vol. 2, no. 11, 1993, OXFORD UNIVERSITY PRESS, UK, pages 1915-1920, XP002017869 D.M. CHURCH ET AL.: "Identification of human chromosome 9 specific genes using exon amplification" see the whole document ---	1-29
A	NATURE GENETICS, vol. 6, January 1994, NATURE PUBLISHING CO., NEW YORK, US, pages 98-105, XP000608940 D.M. CHURCH ET AL.: "Isolation of genes from complex sources og mammalian genomic DNA using exon amplification" cited in the application see the whole document ---	1-29
A	WO 92 13071 A (MASSACHUSETTS INST TECHNOLOGY) 6 August 1992 see the whole document ---	1-29
A	DE 40 21 458 C (MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN) 29 August 1991 see the whole document ---	1-29
	-/--	

BNSDOCID: <WO___9748797A1_I_>

INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/US 97/00785

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CELL, vol. 75, 31 December 1993, CELL PRESS,CAMBRIDGE,MA,US;, pages 1305-1315, XP002017870 THE EUROPEAN CHROMOSOME 16 TUBEROUS SCLEROSIS CONSORTIUM: "Identification and characterization of the touberous sclerosis gene on chromosome 16" cited in the application see the whole document ---	1-29
A	CELL, vol. 77, 17 June 1994, CELL PRESS,CAMBRIDGE,MA,US;, pages 881-894, XP002017871 THE EUROPEAN POLYCYSTIC KIDNEY DISEASE CONSORTIUM: "The polycystic kidney disease 1 gene encodes a 14kb transcript and lies within a duplicated region on chromosome 16" cited in the application see the whole document ---	1-29
A	KIDNEY INTERNATIONAL, vol. 43, no. s39, 1993, SPRINGER VERLAG, BERLIN, BRD, pages S20-S25, XP000608988 G.G. GERMINO ET AL.: "Positional cloning approach to the dominant polycystic kidney disease gene, PKD1" cited in the application see the whole document ---	1-29
A	HUMAN MOLECULAR GENETICS, vol. 2, no. 6, 1993, OXFORD UNIVERSITY PRESS, UK, pages 673-676, XP002017872 M.P. DUYAO ET AL.: "A gene from chromosome 4p16.3 with similarity to a superfamily of transporter proteins" cited in the application see the whole document ---	1-29
A	PROC. NATL.ACAD SCI., vol. 92, May 1995, NATL. ACAD SCI.,WASHINGTON,DC,US;, pages 4362-4366, XP002017873 M.A. BROWN ET AL.: "Physical mapping, cloning, and identification of genes within a 500-kb conatining BRCA1" cited in the application see the whole document ---	1-29

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

BNSDOCID: <WO___9748797A1_I_>

C.(Continuation) DOCUMENTS CO[illegible]ERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CELL, vol. 72, 26 March 1993, CELL PRESS,CAMBRIDGE,MA,US;, pages 971-983, XP002017874 THE HUNTINGTON'S DISEASE COLLABORATIVE RESEARCH GROUP: "A novel gene containing a trinucleotide repeat that is expanded and unsrable on Huntington's disease chromosome" cited in the application see the whole document ---	1-29
A	GENE, vol. 161, no. 2, 19 August 1995, ELSEVIER SCIENCE PUBLISHERS,B.V.,AMSTERDAM,NL;, pages 183-187, XP002017875 T.C. BURN ET AL.: "Increased exon-trapping efficiency through modifications to the pSPL3 splicing vector" cited in the application see the whole document -----	1-29

BNSDOCID: <WO___9748797A1_I_>

INTERNATIONAL SEARCH REPORT

l national application No.

PCT/US 97/ 00785

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see continuation-sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-29

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

BNSDOCID: <WO___9748797A1_I_>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Claims: 1-29

Isolated nucleic acid encoding human netrin (hNET) or its complement; isolated nucleic acid that hybridizes under stringent conditions to said nucleic acid; an antisense oligonucleotide that specifically binds to and modulates translation of mRNA of said hNET; isolated human netrin and biological active fragments thereof; a vector comprising said DNA; a host cell comrising said vector; a method for producing hNET; an antibody that specifically binds to human netrin; a transgenic non-human mammal expressing said DNA encoding hNET; a method for identifying compounds which bind to human netrin.

Claims: 30-56

Methods and products as in invention one but limited to human ATPase binding cassette transporter (hABC3) or its complement.

Claims: 57-74

Methods and products as in invention one but limited to human ribosomal L3 (RPL3L) or its complement.

Claims: 75-93

Methods and products as in invention one bur limited to human augmenter of liver regeneration (hALR) or its complement.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna J Application No
PCT/US 97/00785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9702346 A	23-01-97	AU 6386596 A	05-02-97
WO 9513367 A	18-05-95	US 5565331 A	15-10-96
		CA 2174971 A	18-05-95
WO 9213071 A	06-08-92	NONE	
DE 4021458 C	29-08-91	US 5252475 A	12-10-93

BNSDOCID: <WO___9748797A1_I_>